THE American Journal OF Gastroenterology

VOL. 32, NO. 5 NOVEMBER, 1959

Twenty-fifth Annual Convention
Philadelphia, Pennsylvania
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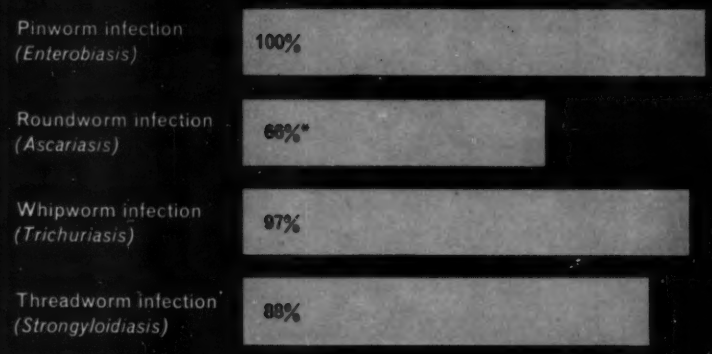

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1. Swartzwelder, J. C., et al.: J.A.M.A., 165:2063, 1957.

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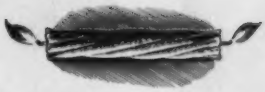

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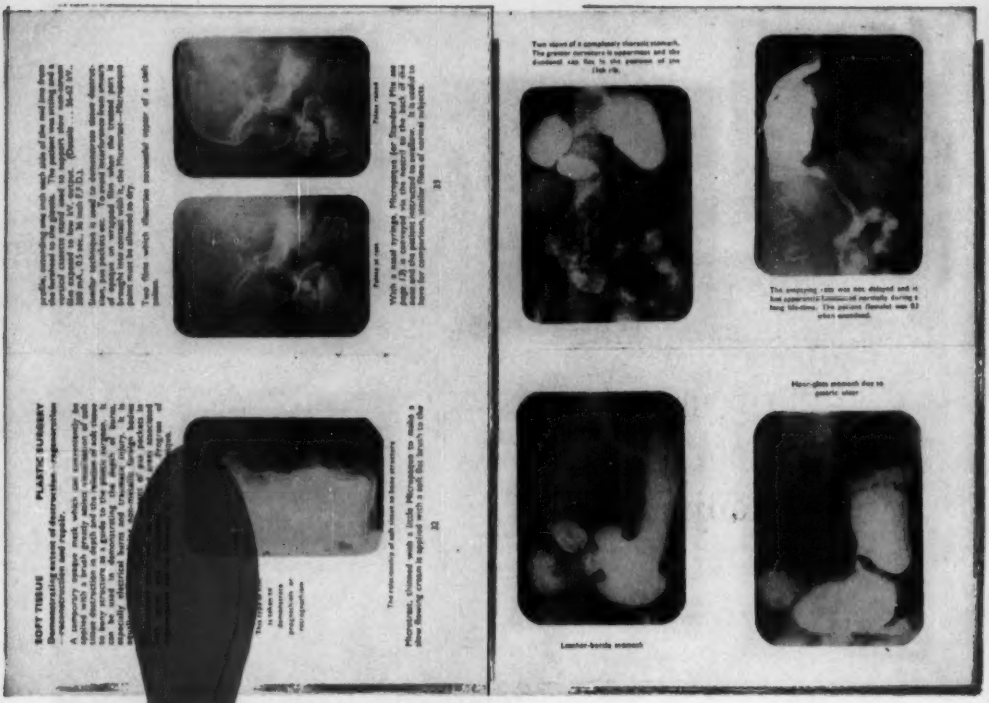

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THE American Journal OF Gastroenterology

(FORMERLY THE REVIEW OF GASTROENTEROLOGY)

The Pioneer Journal of Gastroenterology, Proctology and Allied Subjects in the United States and Canada

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duodenal and gastric ulcer

gastritis

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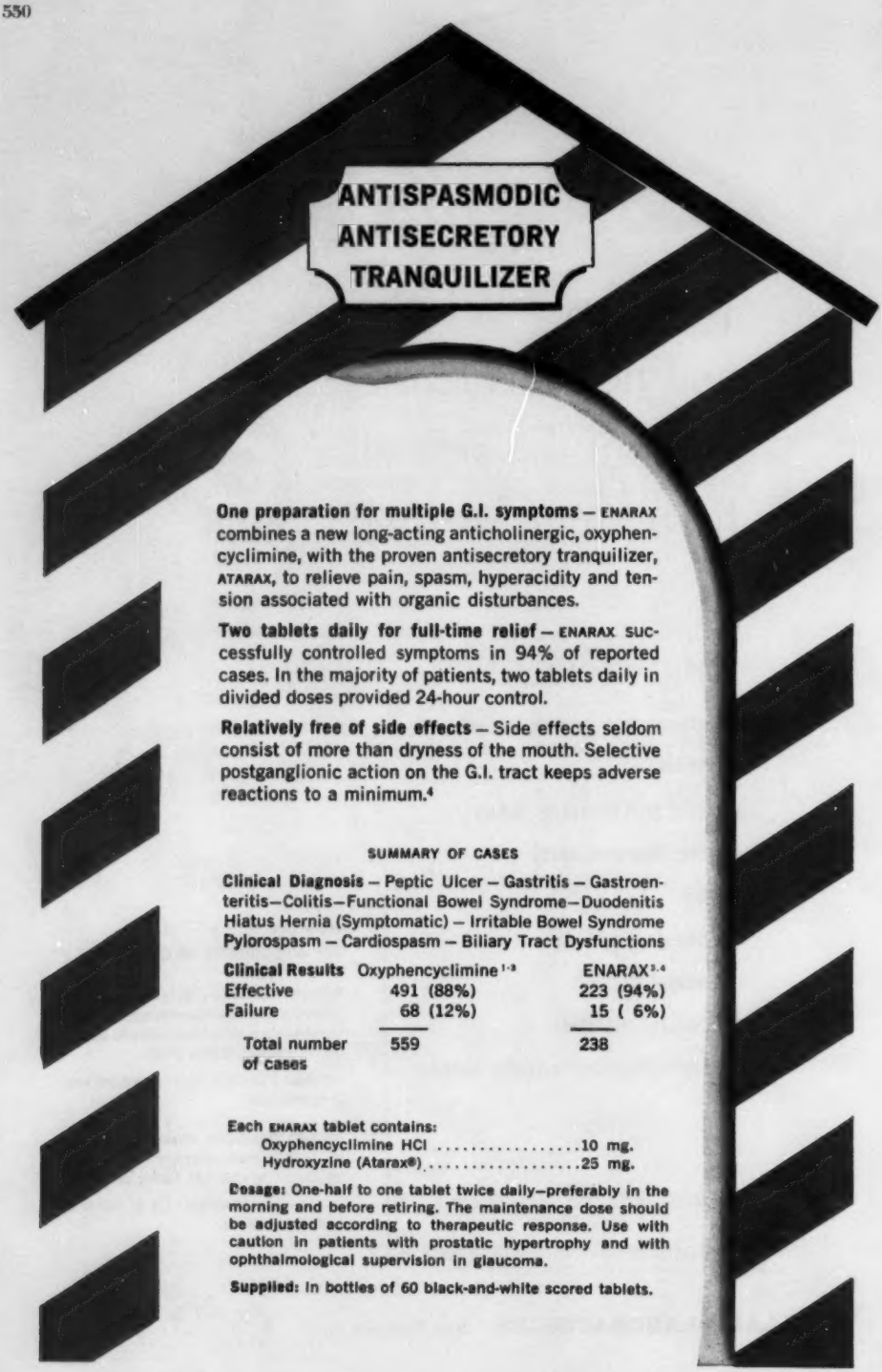

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SUMMARY OF CASES

Clinical Diagnosis – Peptic Ulcer – Gastritis – Gastroenteritis–Colitis–Functional Bowel Syndrome–Duodenitis Hiatus Hernia (Symptomatic) – Irritable Bowel Syndrome Pylorospasm – Cardiospasm – Biliary Tract Dysfunctions

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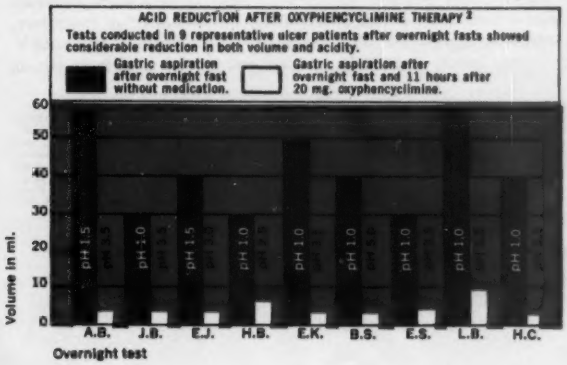

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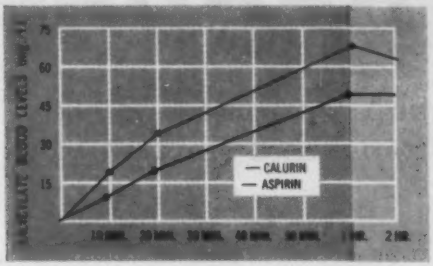

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REFERENCES: 1. Waterson, A. P.: Aspirin and gastric haemorrhage, Brit. M. J. 2:1531, 1955. 2. Douthwaite, A. H., and Lintott, G. A. M.: Gastroscopic observation of the effect of aspirin and certain other substances on the stomach, Lancet 2:1222, 1938. 3. Editorial Comments: The effect of acetylsalicylic acid (aspirin) on the gastric mucosa, Canad. M. A. J. 80:47, 1959. 4. Muir, A., and Cossar, I. A.: Aspirin and ulcer, Brit. M. J. 2:7, 1955. 5. Muir, A., and Cossar, I. A.: Aspirin and gastric haemorrhage, Lancet 1:539, 1959. 6. Schneider, E. M.: Aspirin as a gastric irritant, Gastroenterology 33:616, 1957. 7. Bayles, T. B., and Tenckhoff, H.: Salicylate therapy in rheumatic diseases, Scientific Exhibit, Ann. Mtg. A. M. A., San Francisco, Calif., June, 1958. 8. Batterman, R. C.: Comparison of buffered and unbuffered acetylsalicylic acid, New Eng. J. M. 258:213, 1958. 9. Cronk, G. A.: Laboratory and clinical studies with buffered and nonbuffered acetylsalicylic acid, New Eng. J. M. 258:219, 1958. 10. Editorial: Aspirin plain and buffered, Brit. M. J. 1:349, 1959. 11. Smith, P. K.: Plasma concentration of salicylate after the administration of acetylsalicylic acid or calcium acetylsalicylate to human subjects, Report submitted to Smith-Dorsey from Dept. of Pharmacology, Geo. Washington Univ. School of Medicine, Washington, D. C., Sept. 5, 1958.

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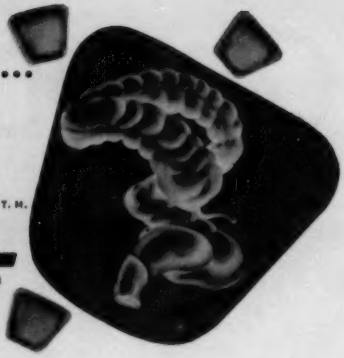

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FORMERLY THE REVIEW OF GASTROENTEROLOGY

VOLUME 32 NOVEMBER, 1959 NUMBER 5

PRIMARY LYMPHOSARCOMA OF THE STOMACH

FIFTEEN YEARS AFTER SURGERY AND RADIATION

JAMES TESLER, M.D., F.A.C.P., F.A.C.G.

and

ABRAHAM J. BRENNER, M.D., F.A.C.G.

Brooklyn, N. Y.

Primary lymphosarcoma is not a common lesion of the stomach. It was stated by various authors that its incidence is about 1.5 to 3.2 per cent of all malignant tumors of the stomach and 1 per cent of all gastric tumors. About 40 to 60 per cent of the sarcomas of the stomach are lymphosarcomas.

We are reporting this case not only from the point of view of survival after surgery, but also in order to emphasize a few clinical, roentgenologic as well as gastroscopic features which may help to establish a preoperative diagnosis.

CASE REPORT

L.B., age 31, male, white, salesman, reported to the office of one of the authors (J.T.) on 8 December 1942, complaining of abdominal pains of three months' duration. At first the patient interpreted these as hunger pains. Later on, the pains occurred daily, at 11 A.M., 3 P.M., and awakened him at night. At times the pains were relieved by the intake of milk and/or food. His appetite was good. Pyrosis was present only when he had the pains. The bowels moved daily. There was no history of nausea or vomiting.

The past history as well as his family history were irrelevant. System review was within normal limits.

Physical examination revealed nothing abnormal except for tenderness in the epigastrium.

The clinical impression was peptic ulcer or possible gallbladder pathology.

From the Departments of Medicine and Gastroenterology, Jewish Hospital of Brooklyn.

On 1 November 1942, the patient had a radiographic study of his gastrointestinal tract, which was reported as negative (Fig. 1).

Cholescystographic examination showed a gallbladder of good concentration and normal evacuation. At the time of this gallbladder study, the patient claimed that for the past few days his stool had been black.

The stomach and duodenum were again x-rayed on 15 January 1943. The films disclosed an ulcer niche on the lesser curvature of the body of the stomach (Fig. 2). The stool examination for occult blood, with the patient on a meat-free diet for 72 hours, was positive.

Fig. 1—X-ray of stomach reported as negative.

Complete bed rest and ulcer regimen were instituted and on 8 February 1943, the stool was still positive for occult blood. Abdominal examination at that time revealed a tender mass in the epigastric region. As a result of these findings, the diagnosis of gastric malignancy was considered and the patient was admitted to the Brooklyn Jewish Hospital on 15 February 1943.

A fluoroscopic and radiographic examination of the gastrointestinal tract was made on 18 February 1943. The findings were reported as suggestive of lymphosarcoma (Fig. 3).

Gastroscopic examination (performed by J.T.) on 19 February 1943, disclosed the following:

The angulus and pyloric opening were seen. The mucous membrane in that area was edematous, thickened and hyperemic. In the antrum, extending to the body of the stomach, one could see a linear thickening, cord-like projection, nodular in appearance, with hemorrhagic areas in the same vicinity. A diagnosis of lymphoblastoma or lymphosarcoma was tentatively made.

Laboratory findings:—Gastric analysis: Free HCl, 0-40 units; Total HCl, 18-65 units.

All gastric specimens were positive for blood. Stools examined for occult blood on two occasions were positive. Red blood cell count and hemoglobin were indicative of secondary anemia.

Fig. 2—The films disclosed an ulcer on the lesser curvature of the body of the stomach.

The patient was operated upon on 26 February 1943, and a subtotal gastrectomy was done.

Pathological report:—The specimen consisted of a sleeve-shaped portion of the stomach measuring 17 x 11 x 4 cm. Six cm. from the pyloric end there was a large defect on the anterior wall measuring 8 x 7.5 cm. The edges of this defect were ragged and arising from them are soft nodules measuring 3 x 2 x .6 cm. The posterior wall contains a large mass measuring 9 x 7.5 x 3 cm. The central portion shows a crater-like depression which is ragged and necrotic. Arising from the base are small polyopid masses. Beyond the tumor mass the mucosa is normal in appearance. At the esophageal end there are only 1.5 cm. of normal mucosa.

Microscopic findings:—The *lamina propria* is edematous and loose with engorged capillaries, with many small round cells, large mononuclear cells,

plasma cells, eosinophils and some polyps. The mucularis is intact. In some places, immediately beneath the mucularis mucosa are fairly well circumscribed zones of tumor tissue. The cells are fairly uniform, have a distinct cell outline, small cytoplasm and large hyperchromatic nuclei. An occasional cell is in mitatic division. The connective tissue stroma is scanty and fibrilar in character. The tumor cells, in places, are seen extending into the muscular coat.

Pathological diagnosis:—Resected stomach—lymphosarcoma.

The patient made an uneventful recovery and was discharged from the hospital on 20 March 1943, and was followed in the gastrointestinal clinic by both authors. He was also referred for radiotherapy.

Radiographic study of the stomach and intestines on 18 May 1943, showed a gastrectomy with only the cardiac end of the stomach remaining. The barium poured readily through the ostium into the jejunum, the coils of which filled well. The progress of the meal at 6 hours was normal.

Until September, 1944 the patient remained symptom-free, when he began to suffer from pains in the lower left back radiating down to the left thigh, leg and foot. There was no change in motor or sensory power. Physiotherapy was then instituted and the pains cleared up in two weeks.

In January, 1946, the patient again experienced severe pains in the lower left back radiating to the left hip and leg. Radiographic studies of the bones did not reveal any metastases. Deep x-ray therapy was given, however, and the sharp pains subsided.

On 19 May 1947, the patient was readmitted to the hospital because of the difficulty in urination of six days' duration. He also complained of severe pains in the back.

Positive findings on physical examination revealed a postoperative ventral hernia. There were hard, movable bilateral inguinal lymph nodes. Both feet were cold and clammy. Any motion involving the back was painful and difficult.

The clinical impressions were:

1. Lymphosarcoma which had metastasized to the spine.

2. Herniated disc to be ruled out.

3. Cord tumor to be considered.

Urological consultation on 22 May 1947 reported the possibility of a metastatic spread to the spine involving the bladder.

A neurological impression was that of a possible metastatic tumor of the *cauda equina.*

Laboratory data:–22 May 1947, Klein test was negative. Blood sugar, 95 mg. per cent; urea nitrogen, 16.8 mg. per cent; calcium, 9.8 mg. per cent and phosphatase, 1.5 mg. per cent.

X-ray studies (25 May 1947) of the thoracic and lumbar spine and pelvis were reported as negative.

Intravenous urography done on 28 May 1947 revealed normal kidneys, ureters and bladder.

A myelogram performed on 2 June 1947 was reported as a spinal cord block of a diffuse nature which might be associated with the patient's lymphosarcomatous condition.

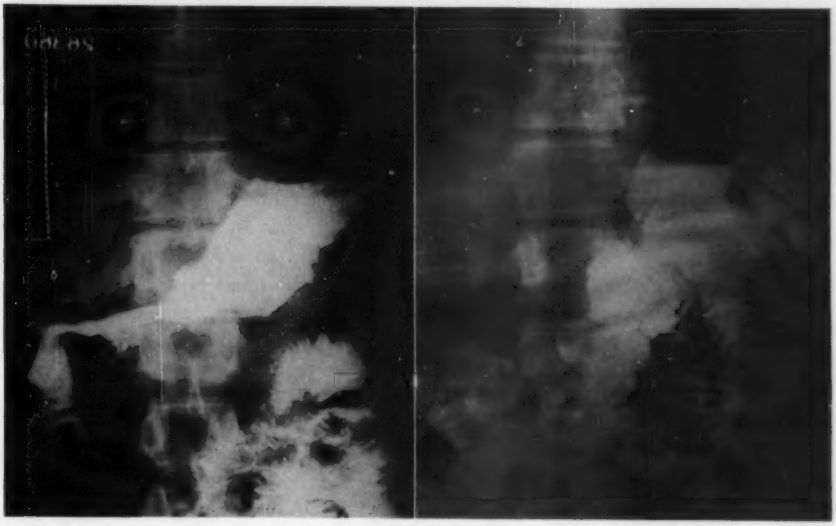

Fig. 3 Fig. 4

Fig. 3–X-ray of the stomach reported as suggestive of lymphosarcoma.
Fig. 4–X-ray film of the stomach was negative except for evidence of subtotal gastrectomy.

A lumbar laminectomy was performed on 6 June 1947. A large retrodural tumor and old blood clot were removed. The pathological report was that of ependymoblastoma.

The patient, however, continued to have pains in the low back and lower extremities with numbness in the lower left extremity. He also had difficulty in urination. On 3 July 1947, a high thoracic cordotomy was done in order to relieve his pains. The patient did well except for some minor postoperative complaints, and was discharged from the hospital on 27 July 1947.

On 6 January 1948, he was readmitted to the hospital. He complained of frequency in urination of two months' duration and occasional pain at the tip of the penis at the beginning of voiding.

Physical examination was negative except for some weakness in the left leg.

Cystoscopic examination revealed pyuria, cystitis and three small calculi. Lithopaxy was performed on 7 January 1948, and the stones were removed. He was discharged on 18 January 1948, in good condition.

Since then the patient has been followed in the various clinics. Numerous x-ray studies of the gastrointestinal tract were done in the hospital as well as in the office of one of the authors (J.T.), and all were reported as negative except for evidence of a subtotal gastrectomy. The last gastrointestinal series was done on 7 March 1958 (Fig. 4).

Discussion

Lymphosarcoma of the stomach is less difficult to diagnose when it is part of a systemic process. When the sarcoma is localized to the stomach the diagnosis is more difficult.

W. T. Snoddy[1] reported 34 cases of primary lymphosarcoma of the stomach and described the clinical features. He states that lymphosarcoma of the stomach has been found by most authors to be more frequent in males than in females. Pain is the chief symptom, usually of the ulcer type and frequently relieved by antacids for short periods. The pain, however, is more persistent and severe than in ulcer cases. The type, character and location of the pain is not of aid in differentiating lymphosarcoma from a benign ulcer or from carcinoma. Vomiting is a secondary symptom as compared to the pain. Hematemesis, when present, may vary from blood-streaked vomitus to one quart of blood. Weight loss of various degrees is present in about 30 per cent. As a rule the patients do not present marked emaciation as is frequently seen in patients with carcinoma of the stomach. A palpable mass is mentioned in about 50 per cent of the reported cases.

According to Kushlan[2] patients with primary lymphosarcoma of the stomach do not present the clinical picture usually associated with carcinoma of the stomach. Their nutrition is usually quite good. The absence of pallor is borne out by the blood count, which tends to be within normal limits or not very far below.

Free hydrochloric acid is usually present in the fasting gastric contents in contrast to its absence in the majority of cases of carcinoma of the stomach. Melena tends to be quite frequent and a careful search will always reveal occult blood in the stool.

Radiographic study of the stomach is considered to be of little value in determining the exact nature of a malignancy of the stomach. Yarnis and Colp[3]

reported eight cases of lymphosarcoma of the stomach. Only in one of the eight cases were the x-ray studies of the stomach suggestive of lymphosarcoma. In only two of the 34 cases reported by Snoddy[1] did the radiologist suggest lymphosarcoma in the description, but a diagnosis of carcinoma was made.

Gastroscopic observations of lymphosarcoma of the stomach have been reported by numerous authors.

Schindler[4] describes the gastroscopic appearance of lymphosarcoma of the stomach as characteristic and almost pathognomonic.

Yarnis and Colp[3] made gastroscopic examinations in five cases of lymphosarcoma and in two of the five the gastroscopic findings were suggestive of lymphosarcoma. They did agree, however, that it was impossible to differentiate the ulcerative or localized polypoid tumors from other malignancies of the stomach, unless a biopsy is performed.

Renshaw and Spencer[5] reported 16 cases of lymphosarcoma of the stomach. Gastroscopic examinations of some of these patients were made. They were unable to single out any characteristics that set lymphosarcoma apart from other malignancies as seen through the gastroscope.

Bockus[6] rightly stated that nothing short of histologic examination can determine the diagnosis of gastric sarcomas. With the use of the combined gastroscope and gastric biopsy under direct vision, a preoperative histologic diagnosis is at times possible.

Comment

The outstanding features of our case were: The patient was only 31 years of age. His complaints were typical of peptic ulcer. The radiographic studies of the stomach at first were interpreted as negative for pathology.

He noticed black stool. X-ray studies of his stomach revealed a niche on the lesser curvature of the body of the stomach. After a strict ulcer regimen with complete bed rest for three weeks, the stools were still positive for occult blood. Abdominal examination revealed a palpable tenderness in the epigastrium. The diagnosis of gastric malignancy was entertained and the patient was admitted to the hospital.

Gastroscopic examination revealed a picture that corresponded to Schindler's[4] description of lymphoblastoma of the stomach. A diagnosis of lymphoblastoma or lymphosarcoma was tentatively made.

Radiographic examination of the gastrointestinal tract was reported as suggestive of lymphosarcoma of the stomach.

A final preoperative diagnosis of primary lymphosarcoma of the stomach was based upon the age, rapid changes in the clinical as well as in the x-ray findings and gastroscopic findings.

At the operation the surgeon's diagnosis was malignant infiltration of almost the entire stomach and he was reluctant to do a resection. Because of the preoperative diagnosis of lymphosarcoma, however, a subtotal resection was done, in the hope that radiotherapy would take care of the rest.

The pathologist gave us the final diagnosis of lymphosarcoma of the stomach. At this point we wish to reiterate Bockus'[6] statement that nothing short of histologic examination can determine the diagnosis of gastric sarcoma.

The palpable mass did not change the prognosis. D. B. Butler and J. A. Bargen[7] in their study of abdominal masses came to the conclusion that in lymphosarcoma of the gastrointestinal tract the presence of a palpable mass implied almost twice as good an outlook as in cases without a palpable mass.

The treatment of choice remains subtotal gastrectomy followed by post-operative roentgen therapy.

It is noteworthy that the arthritic manifestations, spinal cord symptoms and urological condition which the patient developed following the operation were all independent and not metastatic from the lymphosarcoma of his stomach.

Summary

1. A case of primary lymphosarcoma of the stomach who has remained well for more than 15 years after gastric resection followed by radiotherapy is recorded.

2. Clinical and x-ray as well as gastroscopic features were discussed as to their value in arriving at a preoperative diagnosis.

3. The conclusion to be drawn from such a case is that no gastric neoplasm should be considered hopeless in the absence of a laparotomy and microscopic examination.

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DIAGNOSIS OF GASTROINTESTINAL BLEEDING BY MEANS OF SPECIAL TUBE

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Gastrointestinal bleeding is an important symptom of disease. The management of this condition requires the skill and knowledge of an experienced physician. Its onset may be insidious or dramatic. A thorough investigation is required before definitive therapy can be instituted.

The causes of gastrointestinal bleeding are numerous. Bockus[1], Brick[2] and others list the various causes. In all the lists there are varying numbers of cases whose causes are unknown. This varies from six to eight per cent.

Laparotomy as a final resort can be a futile procedure. Bleeding from causes other than peptic ulcer are associated with the highest mortality. These cases offer the most serious diagnostic problems. They require individual management of each case. Generalization can be disastrous. Failure to determine the cause of bleeding may be due to several factors.

1. Localization:—A high ulcer, localized at the fundus of the stomach and a lesion in the small intestine are easily overlooked.

2. Type of lesion:—A superficial lesion (such as hemangioma, superficial ulceration, varicosities) is missed on x-ray, even under the most favorable conditions.

The causes of failure for determination of the source of bleeding in these conditions by the usual gastrointestinal series and barium enema are mainly due to:

1. Failure to recognize the level of bleeding, in x-ray studies with barium. The attention of the physician is distracted from the involved part.

2. Lack of means to control the amount of barium of the part of the gastrointestinal tract under study. The amount of barium varies according to the type of lesion and its localization as will be shown by the experimental work done at this institution.

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The logical way to attack this problem is to determine the localization of the bleeding point and study it under x-ray with barium, the amount of which is controllable.

Experimental Work

A loop of postmortem human intestine, 15 cm. long is pinned to a board. Within it we place a 15-foot long, double lumen tube. This tube has 2 balloons attached, the distal one tied around the end of the tube. The proximal is tied around the tube, 20 cm. apart from the distal balloon. One tube for inflation of air communicates with the balloons. The other tube is for installation of barium between the 2 balloons. A piece of pancreatic tissue is sutured to the mucosa of the bowel in the space between the 2 balloons. The bowel is closed

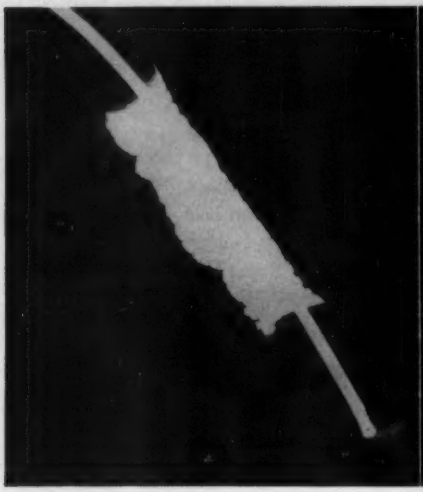

Fig. 1

Fig. 2

and the balloons are inflated with 50 c.c. of air in each. We then injected 50 c.c. of barium into the bowel through the tube. X-ray studies did not show the lesion. Twenty c.c. of barium is aspirated with a syringe. X-ray at this point demonstrates the mass clearly (Figs. 1 and 2).

We conclude that unless the amount of barium instilled at various sites can be controlled, small lesions will be overlooked.

Management of Gastrointestinal Bleeding

With the esophageal tube described in a previous article and the intestinal tube described here, the management of gastrointestinal bleeding should be carried out according to a definite plan.

1. When a patient with gastrointestinal bleeding is admitted to the hospital the esophageal tube is immediately inserted. We are able to determine whether the esophagus is the site of the bleeding[3].

2. If the esophagus is not involved and blood is obtained from the stomach a routine gastrointestinal series is done, when the bleeding is controlled. If we are unable to control the bleeding a blind gastrectomy is performed.

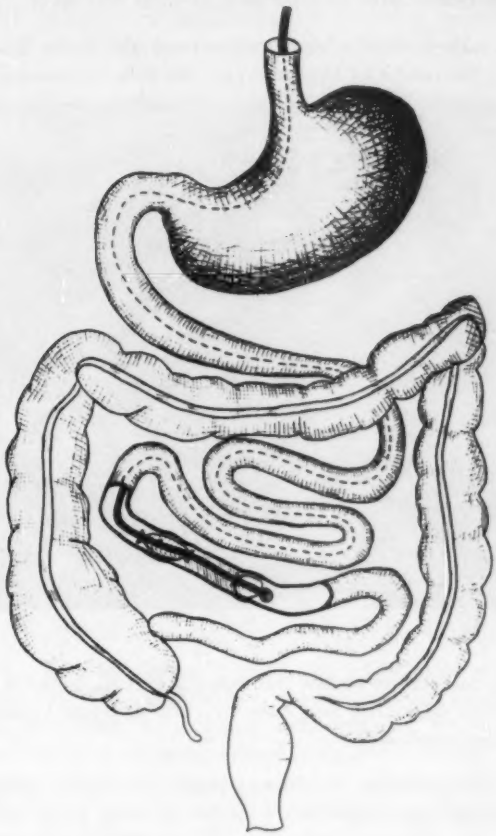

Fig. 3

3. If the gastrointestinal series is negative, but bleeding from the stomach is still suspected a high ulcer of the fundus is ruled out by the use of a gastric tube. The latter is similar to the esophageal tube, except that the balloon is larger and the tube is 10 cm. longer. This tube is inserted into the stomach, the balloon is inflated with 400-500 c.c. of air (according to the size of the

stomach) and is placed in the *pars media*. The fundus is now closed off from the rest of the stomach. Fifty c.c. of barium is injected. X-ray is taken in Trendelenburg's position.

4. If the upper gastrointestinal tract, esophagus and stomach are negative, the intestinal tube is used (Figs. 3, 4 and 5). Keeping always in mind the purposes of the tube, i.e. the determination of the level of bleeding and the x-ray study with controllable amount of barium at this level.

When this tube is used certain precautions are to be taken. In order to avoid trauma to the nose and hypopharynx, the tube is inserted carefully using the following technic: Attach a number 10F catheter to the distal tip of the

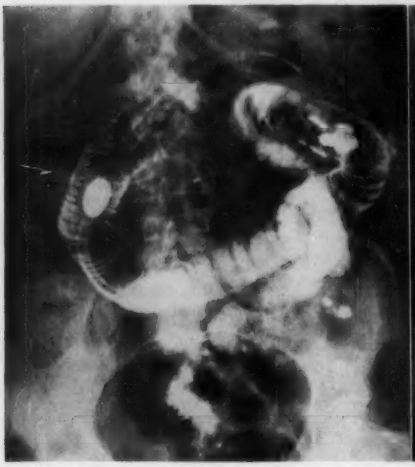

Fig. 4

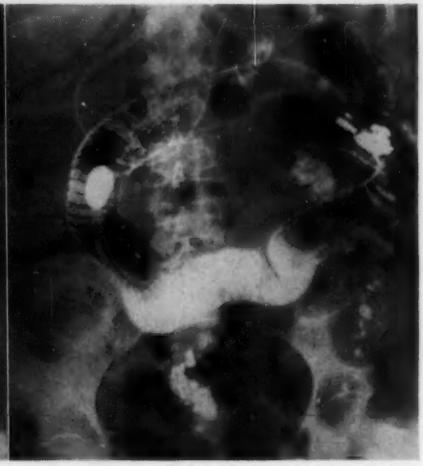

Fig. 5

tube. When this catheter is visible through the mouth, grasp it, detach it from the long tube. Now direct the long tube into the pharynx. Continue to pass the tube as the patient swallows.

To pass a tube into the duodenum place the patient with his right side down, inject through the lumen 10 c.c. of 0.5 per cent HCl. This causes relaxation of the pyloric sphincter. The tube can generally be passed into the duodenum within one hour. At this time an x-ray for position of the tube is taken. From this point on the tube is passed gradually (10 cm. every half-hour.) A specimen of the intestinal content is aspirated at various levels, to ascertain if there is any fresh bleeding. Specimens are kept in separate tubes. Each is labelled to show the level of the gastrointestinal tract. This makes for a good comparison. In case of doubt, Guaiac's test is done on the aspirated specimen.

At the level where fresh bleeding is encountered, the tube is taped to the nose, the two balloons are inflated. Barium is then instilled through the lumen into the intestinal loop between the two balloons. Use small amounts of barium (20 c.c.). X-rays are then taken. If a mass or ulceration is present it will be outlined. If this fails to demonstrate the lesion the tube is advanced to the ileocecal valve. Segmental studies are performed in retrograde manner. It is not anticipated to outline the lesion under the best circumstances if the lesion is superficial. The level of the bleeding, however, is approximately localized, this alone is of great help for the surgeon during his exploration, as noted in Case 3.

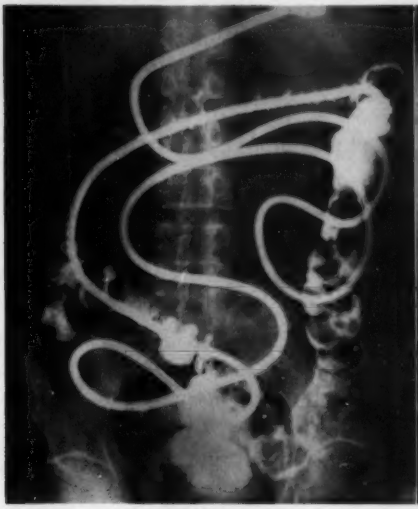

Fig. 6

Fig. 7

Case 1:—F. L., first admission, 54-year old white male admitted to this hospital for melena. There was no history of ulcer, alcohol ingestion or weight loss. The bowel movements had always been regular. Physical examination revealed a well-developed undernourished male with marked pallor of the skin. Examination of the heart revealed a regular sinus rhythm with grade 1 apical systolic murmur. The liver and spleen were not palpable. Temperature 100, blood pressure 110/70, pulse 110.

Laboratory studies:—Hematocrit, 32 vol. per cent; hemoglobin, 9 gm.; RBC, 2,500,000; WBC, 8,500 with 70 per cent neutrophils; 27 per cent lymphocytes; 2 eosinophils; 1 basophil and 1 monocyte. The liver tests were negative. Blood urea nitrogen 22 mg. per cent. Blood sugar 100 mg. per cent. Urinalysis was negative. Stool specimens were port wine in color and showed 4 plus Guaiac test. The gastrointestinal series and barium enema and chest x-ray were negative.

On the 7th hospital day the patient was explored. The stomach, duodenum and jejunum were negative. The ileum contained fresh blood. During the exploration patient had cardiac arrest. He was resuscitated. The exploration was abandoned. During the postoperative period patient stopped bleeding and was discharged in good condition.

Second admission (3 years later):—In the interval there continued to be occult blood in the stool. Several transfusions were required. On the day of admission patient had a bout of massive rectal bleeding and went into shock. Physical examination revealed a man in acute distress with extreme pallor and marked dyspnea. The blood pressure was 70/40, pulse was 135 and very weak.

Laboratory studies:—Hemoglobin was 4.5 gm. per cent; RBC, 1,200,000; WBC, 15,000 with normal differential count; hematocrit was 22 per cent; blood urea nitrogen 30 per cent; blood sugar 105 mg. per cent. Liver profile was negative. After transfusion of 10 pints of blood patient appeared to be stabilized. He still had moderate melena.

The intestinal tube was then passed as described above. Fresh bleeding was aspirated 20 cm. above the ileocecal valve. Thirty c.c. of barium was instilled and x-rays were taken (Fig. 6). This revealed a small diverticulum.

On the 10th hospital day the patient was explored. A Meckel's diverticulum with ulceration of an ectopic gastric mucosa was found. A resection of the small intestine with end-to-end anastomosis was performed. The patient had an uneventful recovery and was discharged on the 21st hospital day. He was seen in the Out Patient Clinic on several occasions and over a period of 3 years there has been no melena. The hemoglobin has been maintained at the normal level.

Case 2:—A 47-year old white female entered this hospital because of tarry stools. She had been subjected to postprandial pain for the last four years. A gastrointestinal series was done by the family physician and revealed a gastric ulcer. She was treated with ulcer diet, antacids and parasympathicolytic medications, with no apparent relief of symptoms. On the day of admission she noted tarry stools, felt weak and dizzy. The physical examination revealed a well developed, well nourished female with marked pallor of the skin. Heart and chest were negative. Liver and spleen were not palpable. Abdomen soft, flat and presented no masses. Pelvic examination was negative. Temperature, 100; pulse, 120; blood pressure, 120/65; hemoglobin, 8 gm. per cent; RBC, 2,200,000; WBC, 8,500; hematocrit, 35 vol. per cent; blood urea nitrogen, 24 mg. per cent; urine, negative. Stool specimens were tarry in color and showed 4 plus Guaiac.

The esophageal tube was passed on admission. There was no blood in the esophagus or stomach. The gastrointestinal series showed a chronic duodenal ulcer. Because of the absence of blood in the stomach on admission segmental

studies of the small intestine with the intestinal tube were carried out. The tube was passed. There was no blood in the stomach or duodenum. At the proximal end of the jejunum fresh bleeding was obtained. The 2 balloons were inflated and 20 c.c. of barium was instilled. X-ray at this level was negative. The tube was advanced to the ileocecal valve and retrograde segmental studies were done, but there were no demonstrable abnormalities present. We were satisfied, however, with the determination of the level of the bleeding, and we decided to explore the patient. On exploration there was a chronic cholecystitis. The gallbladder was intimately adherent to the first portion of the duodenum accounting for the deformity that was visualized in the gastrointestinal series. After the gallbladder was freed the duodenum and stomach were carefully examined. There was no evidence of ulcer or other pathology, except for the periduodenitis secondary to cholecystitis. The exploration of the small intestine revealed the presence of fresh bleeding in the proximal part of the jejunum at the level where the blood was obtained through the intestinal tube. Two hemangiomas measuring 2 x 2, 5 cm. each were found. A small bowel resection with end-to-end anastomosis and cholecystectomy were performed. Patient had an uneventful recovery, had no pain or melena for the last 26 months.

Case 3:—A 48-year old white female was admitted to this hospital for shortness of breath, weakness, dizziness. Patient stated that three months prior to admission she started to feel weak and had several dizzy spells and occasional attacks of precordial pain on exertion. There were no symptoms referred to the gastrointestinal or genitourinary tracts. Her menstrual periods which were always normal, had started when she was 14 years old and ended when she was 46.

The physical examination revealed a well developed, well nourished pale female, moderately dyspneic. There was no congestion or pulsation of the neck vessels. Heart showed regular sinus rhythm, a grade 1 apical systolic murmur. Liver and spleen were not palpable. Abdomen was soft and flat. There were no palpable masses. Pelvic examination was essentially negative.

Laboratory studies:—Hemoglobin, 7.5 gm. per cent; RBC, 2,000,000; WBC, 9,500, with normal differential; blood sugar, 95 per cent; blood urea nitrogen, 12.5 mg. per cent. Liver profile was negative. Urinalysis negative. Stool specimens revealed tarry stools and showed 3 plus Guaiac test. Electrocardiogram showed myocardial ischemia with left ventricular strain, x-ray of chest was negative.

No blood was obtained from the esophagus or stomach from aspiration through the esophageal tube. The gastrointestinal series and barium enema were negative. Segmental studies of the lower gastrointestinal tract were carried out with the intestinal tube. A diverticulum of the second portion of the duodenum was found (Fig. 7). This lesion did not show up on the original

x-ray. After the patient was tranfused she was explored. The stomach, small and large intestines presented no abnormalities except for a large diverticulum localized at the second portion of the duodenum measuring 3 cm. in its greatest diameter. The latter was resected and the duodenum was closed in the routine manner. Since then patient has been symptom-free over a period of three years.

It is oft times very difficult to explore an abdomen for gastrointestinal bleeding and then have to back away because of failure to locate the source.

Conclusion

We are reporting a new type of tube to aid in the diagnosis of the source of bleeding from the gastrointestinal tract. While the procedure is complicated and time-consuming we feel that any modality that increases the percentage of diagnosis is valuable.

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BARIUM FECALITHS FOLLOWING GASTROINTESTINAL RADIOGRAPHY

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The accidental finding of barium fecaliths in the rectosigmoid of two patients, in both instances more than one year after barium studies, served as a stimulus for this investigation. One of these patients, a woman of 62 had her upper gastrointestinal tract and colon studied because of severe constipation. The other, a female of 67, had a barium enema examination following colostomy. No laxatives or cleansing enemas were given following those examinations and no further barium studies were made in the interval. The presence of large semisolid barium sulfate fecaliths was established by radiographic examination of the abdomen and all were removed by the use of rectal instruments (Figs. 1 and 2). In view of the importance of the above occurrences it was decided to investigate the time necessary for the average patient to evacuate the barium introduced orally or rectally without the use of laxatives or enemas.

Material and Methods

One hundred patients, 50 female and 50 male, between the ages of 13 and 77, who submitted to gastrointestinal examinations, were chosen at random for this investigation. Their average age was approximately 50 years. Twenty-five of them had previous barium studies and none of these were found to have residual barium in the alimentary canal as shown by a preliminary flat plate of the abdomen. From this group of 100 patients, 56 had upper gastrointestinal studies, 29 barium enema examinations, and 15 both. After the completion of the recent studies all patients were instructed to avoid taking any laxatives or use any cleansing enemas and return to the X-ray Department for an additional flat plate of the abdomen in one week.

Results

None of the 100 patients examined were found to have any obstructive lesions within the gastrointestinal tract. Fifty-seven of them (32 male and 25 female) were free of barium at the end of the first week. Thirty others were found to have small amounts of barium mixture in the appendix and colonic

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diverticula. Retention of barium in the appendix was more common in men, while retention of barium in the diverticula predominated in women. Five patients were found to have small amounts of barium mixed with fecal matter throughout the colon. Four patients retained barium in the cecum and descending colon. In another 4 patients, barium was found to be collected within the rectosigmoid colon. None were found to have retained barium in the upper gastrointestinal tract at the end of the first week. All the above 43 patients that had retained barium in the colon after the first week were subjected to weekly examinations of the abdomen, and only 4 of them were found to have retained

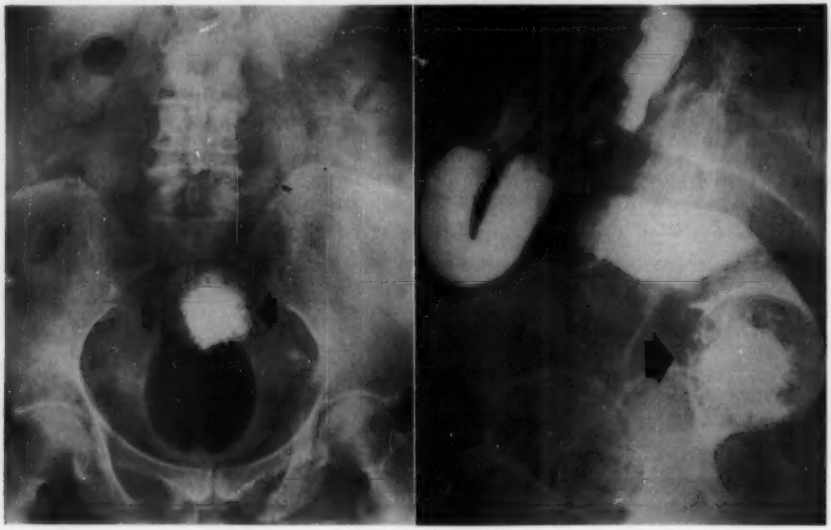

Fig. 1a Fig. 1b

Fig. 1a—A.P. view of abdomen showing barium fecalith one year after upper gastrointestinal tract study and barium enema. Patient manipulated fecalith with her finger in order to move her bowels.

Fig. 1b—Lateral view of same case after instillation of portion of barium enema mixture. This demonstrates mobility of bariolith. In Fig. 1a it was in midrectum above retention catheter balloon and is now seen in distal rectum just above sphincter.

negligible amounts of barium in colonic diverticula at the end of the fourth week. In other words, 96 per cent of the patients examined had completely expelled the barium mixture within a month. It is therefore apparent that the average patient will evacuate the barium administered orally or rectally within at least one month, and the majority of them within a few days. Regardless of the mode of administration, the rate of expulsion of barium is almost the same. The retained barium in the right colon was solely seen in women. Females also predominated in the retention of barium throughout the colon and rectosigmoid.

Comment

While almost all workers in the field of gastrointestinal roentgenography are acquainted with the constipating effect of administered barium sulfate suspensions, few have discussed this phenomenon in the medical literature. A review of the American and foreign literature over the past 10 years is remarkably sterile in this respect. Most articles mention barium inclusions of the appendix[1,2]. Valladares describes 10 cases of barium fecaliths which he observed and suggests the term "bariolite" to designate the barium concretion which forms in the gastrointestinal tract[3].

Shanks and Kerley[4] in their discussion of the technic of the barium meal advise against use of aperients when studying the small bowel and colon from above, with the following exception: "In cases of severe colonic stasis, however,

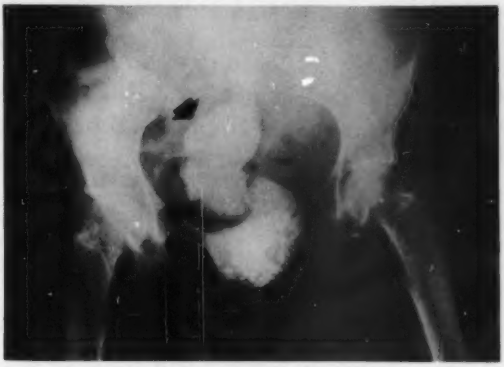

Fig. 2–Fecalith in rectum and sigmoid one year after barium examination of distal limb of colon through colostomy opening.

this rule cannot be applied for too long. With each succeeding day, if no action of the bowels takes place there is an increasing inspissation of the barium with formation of scybala, and if a partial organic obstruction be present in the left half of the colon, a serious exacerbation may result from neglect of this point."

Bockus[5] states that 5 per cent of the patients submitted to gastrointestinal examinations requiring the use of barium may form fecaliths. This investigation, however, has shown no fecalith formation and no barium retention after a month's time. The unusual findings of fecaliths in the two patients originally mentioned resulted from some abnormality of the gastrointestinal tract. The fact that all 100 patients examined had practically expelled the barium mixture at the end of one month indicates that examinations of this nature are rather harmless and will not result in fecalith formation. It is felt, however, that in all patients and especially in the presence of severe constipation and senility, a laxative and/or a cleansing enema is recommended.

Care must be exercised in cases of obstruction, particularly with lesions in the left half of the colon. In all situations in which the gastrointestinal tract is examined with the aid of barium suspensions and in which there is a possibility of colonic obstruction, one should perform a barium enema first, before administering barium orally.

Conclusions

One hundred patients undergoing upper gastrointestinal or enema studies with barium were examined at weekly intervals with the purpose of determining the rate of evacuation. Fifty-seven per cent of patients examined were free of barium at the end of the first week. The remaining 43 per cent expelled the barium mixture within one month. In no case was there barium fecalith formation. There was no difference in the rate of expulsion between the orally and rectally administered barium sulfate mixture. The formation of fecaliths, in the two women patients originally mentioned, more than one year after gastrointestinal studies, most likely represents some rare disorder of the alimentary tract. It is therefore concluded that in the average patient the formation of fecaliths is most unusual and can be entirely avoided by a careful cleansing of the gastrointestinal tract after barium studies.

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CONGENITAL BILIARY ATRESIA

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Introduction

Liver diseases, in infancy, of diverse etiologies, frequently produce indistinguishable clinical syndromes. Because these conditions may cause irreversible liver damage when treatment is not instituted promptly, early differential diagnosis is mandatory. Congenital malformations of the biliary system are the most serious of the causes, and are occasionally correctible.

Congenital biliary atresia causes early, progressive jaundice, with death due to hepatic failure. Anatomically, this is represented: 1. by absence, in whole or in part, of the biliary excretory system, 2. by destruction of the hepatic parenchyma to a variable extent, and 3. by replacement of the lost parenchyma by scar tissue; the late stage of this replacement is similar to biliary cirrhosis.

The diagnosis of congenital atresia of the bile ducts, has usually been made at laparotomy, solely on gross examination of the structures in the *porta hepatis*. Several factors militate against the complete validity of this procedure. One fact is that the bile ducts are small, delicate and can be easily damaged.

Secondly, the gross appearance of the ducts may be misleading, for they may be present but atretic, or they may look normal in their extrahepatic segments and be atretic within the liver, or they may be present but not be found, as in the case of an aberrant common duct. Finally, laparotomy itself may be hazardous in a small, sick infant.

Because of these facts, the clinical course of the disease, the pathogenesis, and the treatment of biliary atresia have become confused.

It is important that study of the fundamental facts of this disease be retrospective and based upon observation of patients in whom the diagnosis had been incontrovertibly proven by postmortem examination. It is also important to determine that the histologic alterations of the liver were sufficiently distinctive to be identified by needle biopsy in the early days of infancy.

The objectives of our study of biliary atresia are to determine:

1. The natural history of disease.
2. The gross anatomy of the liver and bile ducts.
3. The histology of the hepatic parenchyma.

From the Armed Forces Institute of Pathology.

4. To establish the pathogenesis of the disease by correlation of the pathologic anatomy, and the known facts concerning the embryology of the liver.

5. Retrospectively the study also revealed the feasibility of diagnosis of the disease solely, by examination of the histology of the liver in samples obtained by needle biopsy. The criteria for this are set forth.

Material

The material studied included 60 cases in the collection at the Armed Forces Institute of Pathology, Washington, D. C. (AFIP). Additional material was found in the American Registry of Pediatric Pathology, in the course of an investigation into another problem. This provided histologic sections of liver

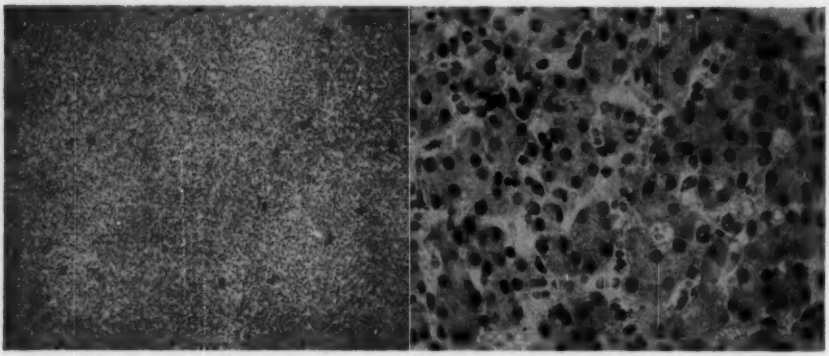

Fig. 1 Fig. 2

Fig. 1—Section from the liver of a newborn infant with congenital biliary atresia. No lobular pattern is apparent. The small collections of dark cells are foci of hematopoiesis. AFIP Acc. 554669. H & E. x70.

Fig. 2—High magnification of Fig. 1. The liver cords are irregular. AFIP Acc. 554669. H & E. x540.

and other data from 170 patients. In all instances the diagnosis was confirmed or established by autopsy.

Clinical Data

General:—There were 60 cases of which 30 were males; 30 females.

All races were represented in numbers proportional to their frequency in the AFIP population.

The occurrence was once in every 300 autopsies (60 cases in 20,000 autopsies).

Three were stillborn and one died at 10 years. The average age at death was six months; median age at death was three and one-half months.

The birth status indicated 27 were full term; 21 were premature; 12 were not designated.

In two cases there was a history of jaundice in siblings. There was no history of familial congenital biliary atresia.

Symptoms:—Jaundice was the presenting symptom in 41 patients. The age at which jaundice was first noted ranged from birth to six weeks. In only two patients was jaundice observed at the time of birth, and in one of these infants severe erythroblastosis was present in addition to the biliary atresia. Jaundice was not evident at any time in the 13 patients whose ages at death were from one hour to 53 days. The three stillborn infants with biliary atresia were not jaundiced.

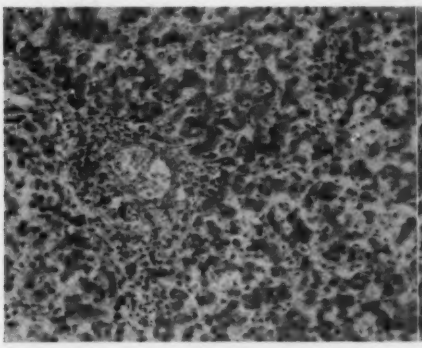

Fig. 3

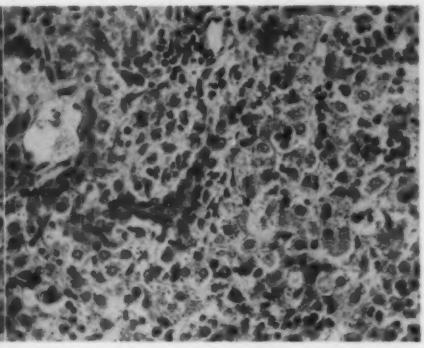

Fig. 4

Fig. 3—Portal space without recognizable bile ducts, 4 day old infant. AFIP 5619625 H & E. x190.

Fig. 4—An "afferent" ductule from a normal liver of a newborn. Note how the epithelial cells blend in with the hepatic cells. AFIP Acc. 5520364. H & E. x400.

Feces were acholic and the urine was dark in all patients who lived sufficiently long for these observations to be made. The notation that the "meconium was not believed to be abnormal", was found on many charts. Severe anemia developed in all patients who survived longer than two months. In two patients, clinical manifestations of the anemia secondary to the bile duct atresia were the presenting symptoms.

Clinical Course

Generally, the course of these patients was marked by failure to grow or to gain weight, by difficulties in hydration and feeding, by deepening jaundice, and finally by death in hepatic coma or from an intercurrent infection. Occasionally the course fluctuated and there were periods in which jaundice was not obvious and the general condition was good. In the children who survived

beyond one year of age, ascites and signs of portal hypertension were frequently seen. Death in this group often resulted from rupture of esophageal varices.

Laboratory data:—Serum bilirubin levels were elevated in all patients from 4 to 27 mg. per cent. The indirect van den Bergh usually was greater than the direct. The values for serum bilirubin fluctuated widely in almost all the patients, but the proportion of direct to indirect bilirubin usually remained constant for the same patient. Despite fluctuations, the average bilirubin levels over a long period were high. The thymol turbidity and cephalin flocculation tests generally were weakly positive, frequently negative, and in only one patient were they both strongly positive.

Bile was present in the urine of all patients. Fecal bilirubin was absent, or present in slight traces. In three patients fluctuating amounts of fecal bilirubin were measured at different times, but never were normal levels observed.

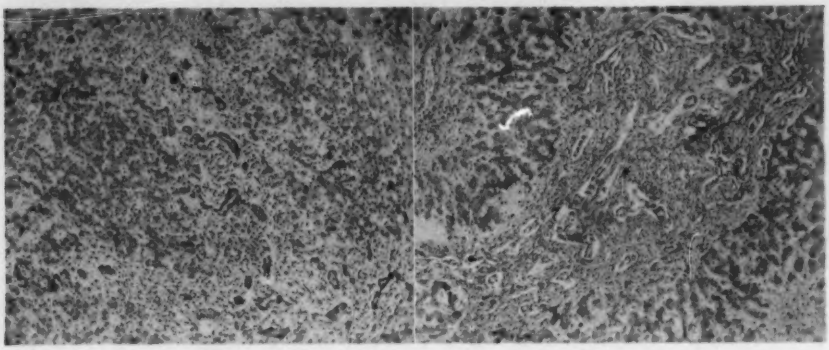

Fig. 5 Fig. 6

Fig. 5—Proliferation of afferent ductules in biliary atresia. AFIP Acc. 572611. H & E. x115.
Fig. 6—Proliferation of bile ducts within the portal space in biliary atresia. AFIP Acc. 572605. H & E. x90.

Coincidental congenital malformations:—Fifteen (25 per cent) of the patients had one or more congenital anomalies in addition to their hepatic disease. Generally, members of this group died early in the neonatal period. The children who survived longer than three months had no additional malformations. There was no correlation between any specific anomaly and congenital biliary atresia. The malformations found were:

Congenital heart disease, 4

Imperforate anus, 4

Atresia of the duodenum, 4

Polycystic kidneys, 3

Anencephaly, 2

Mongolism, 2

Tracheoesophageal fistula, 2

Syndactly, 2

In one case each, hydrocephalus, myelomeningocele, absence of the corpus callosum, cyst of the septum pellucidum, atresia of the colon, annular pancreas, hypoplasia of the kidneys, horseshoe kidney, agenesis of the adrenals, failure of lobulation of the lungs, pseudohermaphroditism and supernumary digits were found.

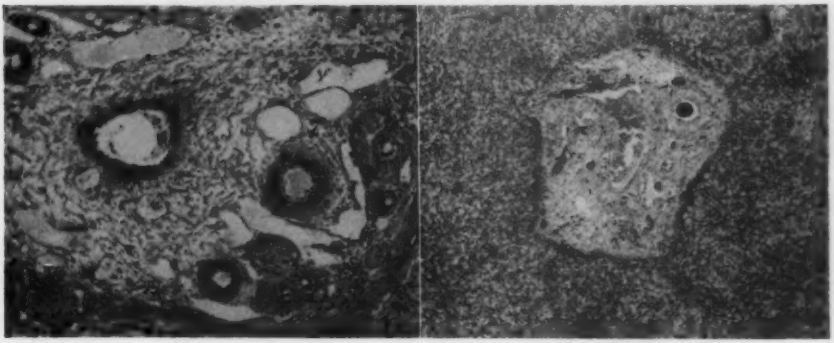

Fig. 7 Fig. 8

Fig. 7—Hypertrophy of branches of the hepatic artery in biliary atresia. AFIP Acc. 572608. H & E. x120.

Fig. 8—Congenital biliary atresia in a 1,200 gm. stillborn infant. The branches of the hepatic artery are hyperplastic. Bile ducts are present here, but this infant had no extrahepatic biliary tree. AFIP Acc. 578720. H & E. x65.

Erythroblastosis fetalis occurred in two patients, in one of whom kernicterus developed. No other patients were found to have kernicterus or manifested clinical signs of neurologic disease.

Anatomic Studies

Gross findings:—In the younger group of 230 patients (birth to 1 month) the size and weight of the liver deviated but little from the accepted normal. In one patient the liver was reduced by 50 per cent and in another it was twice normal weight. In all older patients marked fibrosis, manifested by coarse nodularity of the liver parenchyma and thickening of Glisson's capsule, was evident. Bile staining was also visible, but varied greatly in amount.

Variations in extrahepatic biliary ducts:—Variations in the extrahepatic biliary duct system may be classified as follows (with frequency expressed as per cent of 220 cases):

1. Complete absence of any extrahepatic biliary structures (10 per cent).

2. Partial absence, atresia, or both, of the ducts, (i.e., absence of the common bile duct while the hepatic ducts and gallbladder are present; or fibrous remnants of the duct system following the usual course but without a lumen) (64 per cent).

3. Atresia of the hepatic bile ducts (the gallbladder and common ducts are normal but the hepatic ducts are absent or completely atretic) (11 per cent).

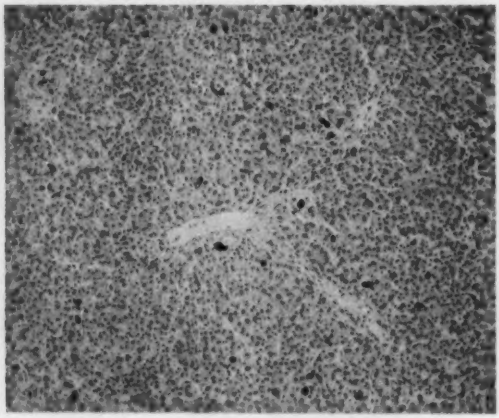

Fig. 9—Isolated stenosis of the common duct. Patient 7 days of age. Relatively large amounts of bile throughout all parts of the lobule are present. The lobular architecture is not otherwise disturbed. AFIP Acc. 57637. H & E. x80.

4. Normal extrahepatic bile ducts with visible atresia of the intrahepatic portions of the large hepatic ducts (7 per cent).

5. No gross abnormalities of the extrahepatic biliary tree; intrahepatic atresia only (5 per cent).

6. Localized stenosis of the common duct, usually at or near the papilla of Vater (3 per cent).

This is a general grouping of the gross malformations observed. In all there were 37 variations noted in this series.

Histopathologic alterations of the liver:—Basic features of the disease are discernible in all specimens. Other changes are secondary to hepatic damage

and scarring and vary with the duration of the disease. The basic abnormalities of the hepatic architecture are those of the microscopic portion of the biliary system, and of the hepatic vasculature. Later secondary effects are fibrosis, cirrhosis and bile stasis.

Abnormality of hepatic architecture:—The entire hepatic parenchyma lacks the usual lobular pattern. Microscopy reveals lack of regular relationship between portal spaces and central veins (Fig. 1) and irregular alignment of cells and cell cords within the lobules (Fig. 2). In the liver of the young infant, even in normal infants, bile ducts may be hard to find; the small size of the specimen

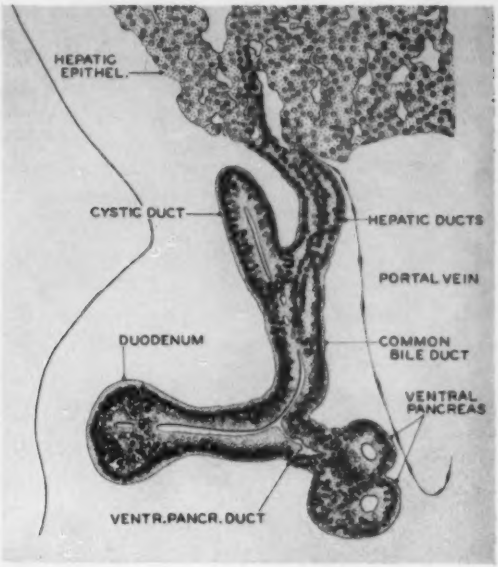

Fig. 10—Early development of biliary system. The differentiation of hepatic cells into bile duct epithelial cells begins in the hilar region. x200.
(Reproduced from Streeter: *"Developmental Horizons in Human Embryos,"* by courtesy of the Carnegie Institution of Washington).

may cause difficulty in the evaluation of the over all pattern, and fibrosis and bile stasis are seldom seen in the early stages of the disease.

Abnormalities of intrahepatic bile ducts:—The small bile ducts may be absent (Fig. 3), but this is relatively rare. More often proliferation of duct epithelium is seen in the portal spaces. This proliferation may involve either of two separate sets of ducts. We identify *afferent* ductules (leading from the lobules to the portal space) and efferent ductules (leading away from the portal space).

The efferent ductules are transitional structures which connect the hepatic cell and the definitive bile ducts. This is reflected in the cellular character of the epithelium, which resemble hepatic cells at the lobular terminus and is like the bile duct epithelial cells at the portal end of the ductule (Fig. 4). In biliary atresia these ductules may extend for varying distances into the portal space. Their greatest ramifications closely resemble large bile ducts (Fig. 5). Usually, small bile thrombi are visible in the lumens.

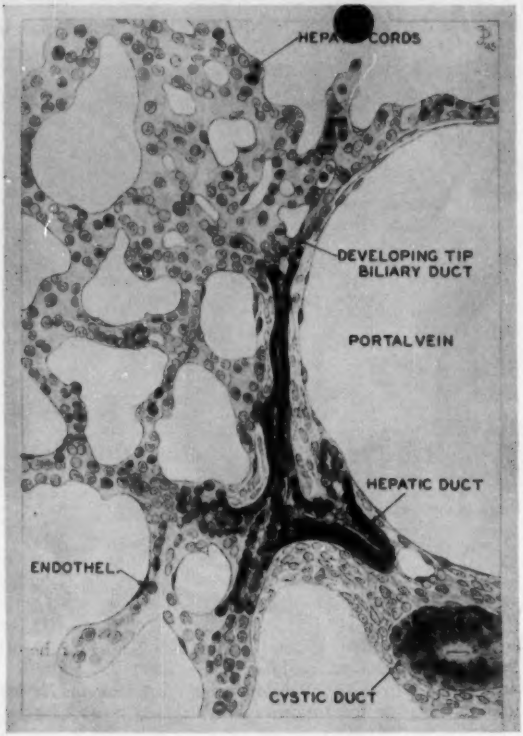

Fig. 11—Transition from biliary ducts to hepatic epithelium. x200.
(Reproduced from Streeter: *"Developmental Horizons in Human Embryos,"* by courtesy of the Carnegie Institution of Washington).

Microscopically, the efferent ducts in biliary atresia may be normal. Variations in the size and shape of the epithelial cells and nuclei with loss of polarity of the nuclei, however, are more often evident (Fig. 6). Usually these ducts do not contain bile. Proliferation of the efferent bile ducts is seen as an increase in the number of ducts within the portal space.

The histologic appearance of the ducts within the liver is not correlated with specific types of malformation of the extrahepatic biliary tree.

Abnormalities of hepatic vasculature:—In the normal infant, branches of the hepatic artery, within the portal space, are usually fairly inconspicuous, approximately the size of the bile ducts which they accompany. In 92 per cent of our cases of biliary atresia, the artery is prominent. This prominence is due to increase in both the absolute size of the vessel and the thickness of its walls (Fig. 7). This is an essential part of the malformation and is not a secondary effect, since it is found in stillborn premature infants with biliary atresia (Fig. 8). This one observation is helpful in the evaluation of material obtained by needle aspiration.

Fibrosis and cirrhosis:—Fibrosis occurs rapidly. It is found in patients as early as two weeks of age and it is regularly present in all patients who survive more than four months. Fibrosis begins in the portal areas and eventually leads to biliary cirrhosis. This cirrhosis differs from classical adult biliary cirrhosis only in its irregularity, stemming from the anomalous hepatic architecture. The late stage of the liver in congenital biliary atresia may suggest coarse nodular cirrhosis.

Bile stasis:—Bile stasis is always present in the liver of the older patients, but only occasionally in the younger. It is logical to expect massive deposits of inspissated bile, but actually only small amounts are found. Bile is deposited first at the periphery of the lobule and rarely involves the entire lobule. It may be deposited as small plugs within ductules, if these be present, or within the Kupffer cells. This pattern of bile deposition is distinctly different from that seen in extrahepatic obstructive jaundice, since in the latter, it is first deposited in the center of the lobule. This type of distribution of bile pigment will differentiate "true" intrahepatic biliary atresia from an isolated stenosis of the common duct, or extrahepatic biliary atresia.

Isolated stenosis of the common bile duct:—The malformation of isolated stenosis of the common bile duct causes obstructive jaundice. Bile is first seen in the centers of the lobules, usually in the Kupffer cells, and later is seen as bile plugs in the larger ducts. Bile is found in large amounts (Fig. 9) and may extravasate into the portal fibrous tissue causing an inflammatory reaction. Fibrosis and cirrhosis accompany long-standing disease. There are no alterations in the bile ducts, hepatic artery or gross hepatic architecture, although secondary cirrhosis, bile duct proliferation, and destruction of the bile duct epithelium and apparent obliteration of the artery accompany the later stages of the unrelieved duct stenosis.

Comment

Embryology and histogenesis[1-5]:—The liver is the most precocious accessory organ derived from the gastrointestinal tract. Hepatic cells are definitely differ-

entiated in the 20 somite (4 mm.) embryo and the anlage of the organ can be delineated even before this. The liver arises as a diverticulum of the primitive gut. As these cells proliferate, they intermesh with the mesoblastic cells derived from the surface of the germinal bed of the coelomic tract in the heart region. The mesoderm gives rise to the hepatic vessels and stroma.

From the very start, the caudal part of the hepatic diverticulum is recognizably different from the rest of the primordial liver. It does not take part in the formation of epithelial cords, nor does it participate in the invasion of the coelomic mesoblastic stroma. It is the primordium of the gallbladder and cystic duct. In the 7.5 mm. stage of development, the liver and gallbladder have assumed fairly definite outlines.

Elongation of the two primordia produces a stalk-like attachment of the two organs to the gut. This stalk is the future common duct. Histologically, the epithelium of the stalk is identical with the epithelium of the gallbladder anlage, but embryologically it is continuous with the liver. Since, however, congenital absence of the gallbladder is not necessarily accompanied by malformation of the common duct, it can be assumed that the duct must be derived from the liver anlage.

The growth and formation of the hepatic ducts and the intrahepatic branches of the biliary system have been observed to arise from the hepatic epithelial cells through "differentiation *in situ*"[1]. This is a process of conversion and differentiation of existing cells, rather than a penetration of the liver parenchyma by new cells from the gallbladder anlage (Figs. 10 and 11). The usual textbook description of the development of the duct system indicates that the duct epithelium infiltrates the hepatic parenchyma. This latter description is not adequate nor completely acceptable. Cellular differentiation of the duct system begins in the hilar region and extends to peripheral portions of the liver later in development. Even in the older fetus, roentgenographic studies show the duct system to be incompletely formed[6], and in histologic sections of the liver from such fetuses, large portions of the peripheral parts of the liver contain no discernible ducts. Continuing development of bile duct from the hepatic epithelium is still evident at term. Some ducts have epithelium which at one end is primarily hepatic and at the other end is distinctly ductal. In the older infant and adult, such ducts are not seen.

Quite apart from the differentiation of the ductal cells, is the intrinsic growth of the duct system. Continued growth and elongation of the ducts proceeds uninterruptedly coincidental with the growth of the other hepatic elements.

Etiology and pathogenesis of congenital biliary atresia:—Causes for congenital malformation are generally grouped into genetic and environmental categories. It is the purpose of this paper, in a broad fashion, to relate the

anatomic appearance of the disease with embryologic development of the liver and biliary duct system but not to ascribe a specific etiology to congenital biliary atresia. To do so, mechanisms of development must be discussed.

There is meager evidence for a genetic cause or background in biliary atresia. Many facts, however, may be advanced in favor of some traumatic factor. First there are very few cases of biliary atresia in siblings. Second, structural findings are extremely variable in biliary atresia, whereas, in most malformations on a genetic basis, the structural findings are similar. Third there is a high percentage of correlation when biliary atresia is compared with other malformations which have their origins at different times during embryonic development. Fourth, congenital biliary atresia has not been recognized as part of any definite recurring syndrome.

Most genetic disturbances result in an "all-or-none" appearance of disease. Had the hepatic epithelium lost (or never attained) the ability to differentiate into bile ducts, it would be expected that there would be complete absence of all ducts. Actually remnants of the system, either gross or microscopic, are most often present. In those instances in which there is specific trauma during gestation (or to a known experimental cause), it is known that the exact moment at which the trauma occurred is of prime importance to the appearance of the final malformation, for it is at the moment of differentiation (or greatest activity) that developing tissues are most susceptible to damage by deleterious influences. Consequently, because of the continuous process of differentiation of hepatic epithelium into biliary ducts, the liver is peculiarly vulnerable to insult and consequent malformation throughout embryonic and fetal life.

It is also known that the application of teratogenetic agents need not be prolonged to produce their effects. The total disruptive action of the agent is derived from its action on a vital cell or group of cells at a specific moment which then may have consequent effects on their descendants. It is reasonable, therefore, to presume that the action of a teratogenetic agent on the liver could affect the formation of bile ducts (the point of specific differentiation) during any interval in fetal growth. Because of the inherent potential of the hepatic epithelial cells for differentiation into bile ducts, following the cessation of the action of the teratogen, the ability to differentiate would again assert itself. During the period of action of the teratogenetic agent, there is no reason to believe that the continued growth of the hepatic cells themselves need necessarily be affected, but only their ability to differentiate into bile ducts. Because of this continued growth of the liver during a period of cessation of bile duct differentiation, and because the organization of the liver as a whole is related albeit secondarily to the biliary system, the general architecture of the entire liver would be irretrievably disrupted by an interruption in the formation of bile ducts.

The final anatomic appearance of the liver, following such an occurrence, could be one of several varieties. There could be absence, interruption of malformation of the ducts in all or part of the system, depending upon the time and duration of the disturbing trauma.

The disease involves the entire liver, rather than the bile ducts alone as seen by disruption of the entire hepatic architecture. The hypertrophy of the hepatic artery is interpreted as a reaction to the total hepatic disorder.

Therapeutic considerations:—In almost every large published series of cases of congenital biliary atresia, reports of a few cures by surgical methods are found[7-11]. Although the number of such instances is small, their importance is great, for the implication that must readily, if not logically, be drawn is that if surgical therapy is possible in one case, it is possible in all. Analysis of these cured cases indicates that the lesion in almost all is readily recognizable as a localized atresia of the common duct. The common duct differentiates very early in the development of the liver. It is possible that in the event of trauma at that stage, the subsequent development of the liver might be unaffected, providing that the action of the teratogenic mechanism were of short duration. Prompt recognition of such localized disease is essential for profound damage to the liver occurs shortly after birth and the sequela of such damage are permanent. Identification of this disease by needle aspiration of the liver is possible, and is recommended.

The importance of histologic examination of the liver in the diagnosis of the disease cannot be overemphasized. The lesion is, in a sense, an "ascending" one, if the liver is viewed as "up" and the common duct as "down". "Ascending" indicates that the lesion may exist "higher" in the system, without manifestations "below". For instance, the hepatic ducts may be atretic and the gallbladder, cystic and common ducts may be essentially normal; the lesions may lie completely within the liver and have no manifestations in the extrahepatic biliary tree. The reverse is not true; there cannot be a lesion of the biliary tree, without a continuation or reflection of the disease within the liver.

Physiologic considerations:—The single most fascinating feature of this disease is the ability of these children to survive for relatively long periods. Interference with the outflow of bile in adults leads rapidly to death. That it does not in the newborn, demands revision of certain of the concepts of the physiology of the fetal and neonatal liver. Not only is the excretion of bile apparently not essential to infants, but biliary precursors may be modified through other metabolic processes. The implication may be drawn that infants have a compensatory mechanism for the elimination of bile pigment when the normal excretory system is absent, and that this is not present in the adult. Because these pigments are largely derived from products resulting from destruction of erythrocytes, their production does not cease. As mentioned above, however,

one is always struck by the relatively small amount of bile pigment in the livers of these patients. It seems necessary, therefore, to presume that the liver cells "reject" biliary precursors, or that these compounds pass through another mechanism and may never reach the liver, then being chemically unidentifiable.

Summary

Based upon data from 60 patients with congenital biliary atresia, the natural history of the disease and its variations have been outlined.

Utilizing material from 230 patients, the pathologic anatomy of the disease has been described.

Emphasis has been placed upon the microscopic characteristics of the hepatic component of the disease, for these provide a basis for diagnosis by needle biopsy.

Histologic features in the liver by which congenital biliary atresia may be identified are:

1. disorganization of the usual hepatic lobular architecture
2. increase in size and thickness of the hepatic artery
3. absence, or abnormalities of the intrahepatic bile ducts
4. bile stasis
5. fibrosis eventuating in cirrhosis.

Lesions of intrahepatic biliary atresia are to be differentiated from those of isolated stenosis of the common duct. The stenosis is a surgically correctable lesion.

Needle aspiration of the liver is a good method for early diagnosis of hepatic disease in the infant and newborn.

A theoretical mechanism for the pathogenesis of the disease based upon embryologic considerations is presented.

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THE ACTION OF SI-1236 ON THE EXCRETION OF UROPEPSIN*†

A New Anticholinergic Compound

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and
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Introduction

Numerous reports have been presented during the last few years with reference to the importance of measuring the urinary pepsinogen. This fact points to the value that this type of test possesses for the diagnosis and prognosis of some conditions of the digestive tract, as well as a series of physiopathological correlations of different diseases, the mechanisms of which have been confirmed, at least in part, through the use of this method of analysis.

Since uropepsin is comparable, to a certain degree, with the proportions of measured gastric acidity, a comparison of both methods seems necessary, with the indication of important advantages for the former, especially when the simplicity of obtaining a sample of urine, in contrast with the problems offered by gastric intubation is taken into consideration. The clinical meaning of uropepsin in some diseases, such as peptic ulcer, gastric cancer and, generally speaking, several conditions that are accompanied by gastric achilia, is similar to that of gastric acidity. For these reasons, uropepsin determinations are being used by an increasing number of investigators, even though they do not show any findings of cells, blood, microorganisms, pus, etc., as are shown by examinations of the gastric contents.

The amounts of uropepsin found also show certain peculiarities in some endocrine conditions and are modified by the administration of hormones. After these changes have been studied, important conclusions have been drawn for the treatment of the corresponding patients.

A revision of conceptions, some comments and the practical use of the quantifications of uropepsin in order to demonstrate the anticholinergic effects of a new drug are the reasons of this paper.

General Conception

Uropepsin, also known as urinary pepsinogen, is an enzyme with proteolytic activity, which is found in the urine when it is acidified up to a pH between 1.5 and 3.5.

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†Compound SI-1236 was kindly furnished by the Medical Department of Pfizer de México, S.A., México, D.F.
‡Deceased, January 1959.

This substance was first found in 1860 by Brucke, who studied its proteolytic action, assuming it was pepsin. Later, Grutzner (1881) confirmed the presence of this enzyme in urine through a fibrin method. Afterwards, some sporadic investigations took place on this matter. In 1930, Bendersky suggested the name uropepsin for this compound, in view of its similarity to pepsin. It was not until 1945, thanks to a careful revision by Bucher, that medical attention began to be attracted, becoming the point of departure for many papers which have been contributions to clarify the normal and the pathological meaning of the quantities of uropepsin present, besides suggesting several different methods for its determination, searching for one that has simplicity and accuracy. A uniformly adopted method has to be developed as yet. Nevertheless, the different units can be compared through simple estimations, in the majority of these methods.

Uropepsin exhibits close similarities with pepsin. It has been demonstrated that both compounds have a common predecessor: pepsinogen. Both reach their optimal enzymatic activity in an acid pH and act upon substrata of a similar chemical constitution.

At present, the great majority of investigators are in agreement about the mechanism of formation of uropepsin: the peptic gastric cells secrete pepsinogen, which reaches the gastric lumen in a great proportion. Only 1 per cent enters the blood stream directly, from where it is excreted through the kidney in the form of uropepsinogen. This final step is not clearly understood as yet, although some investigators point to a certain parallelism between endogenous creatinine clearance and pepsinogen clearance, but the tubular role in the resorption of the excreted substances, namely, pepsinogen, is not very clearly known at present. Pepsinogen reaching the stomach (99 per cent) is almost immediately transformed into pepsin through the autocatalytic action of pepsinogen, in the presence of hydrogen ions.

Oral and intravenous pepsin has been administered in several investigations, with the purpose of demonstrating the direct secretion of the peptic cells into the blood stream. No change has been recorded by this method in the secretion of uropepsin. Thus, the possibility of pepsin being its predecessor has been excluded. The introduction of pepsinogen into the blood stream, however, has been accompanied by a fast increase in the excretion of uropepsin. These facts have supported the theory of the endocrine secretion of pepsinogen by the gastric peptic cells, since the presence of this viscus is absolutely necessary to find this uropepsin. When a total gastrectomy has been performed, no traces of peptic activity are found in the urine.

Although the coexistence of a high degree of gastric acidity and the increase in the amount of uropepsin is frequent, this relation cannot be always translated into figures, since the variations that occur are so wide that they do not permit it. Stimulation with insulin or histamine, that generally causes

variations in the pH of the gastric juices, are not accompanied by changes in the amounts of uropepsin; however, hydrochloric acid, in the majority of patients who excrete high amounts of uropepsin, increases considerably under histaminic stimulation.

The factors that cause variations in the excretion of uropepsin under physiological conditions are:

1. Age:—Some investigators have reported their experiences in the sense of a decrease of excretion as age increases, although the corresponding amounts are always kept on the minimal normal levels without going further down if health conditions are normal.

2. Sex:—It has been said that women excrete uropepsin in slightly smaller amounts than men.

3. *Diet:*—Although the ordinary variations in the ingestion of food do not produce any changes, diets with a high protein content provoke an increase in the uropepsin levels in two to three days. On the contrary, fasting makes them decrease.

4:—Contrary to what happens with the degree of acidity in gastric juice, pregnancy produces a slight increase in uropepsin amounts; after partum, these amounts decrease rapidly, until they reach the average limits. Premenstrual and menstrual phases also produce slight increases.

5:—Some variations are recorded in the course of the day. It has been pointed out that excretion is higher between 4 P.M. and 9 P.M. and that the lowest amounts are recorded from 11 A.M. to 4 P.M.

6:—Vagal stimulation produces, in the opinion of some investigators, an increase in the excretion of uropepsin. We also know, from observations of Gray and co-workers, that acute stress conditions, such as the imminence of a surgical operation, traumatic accidents like burns and others which produce pain, etc., cause a considerable increase in the excretion of urinary pepsinogen. These two facts furnish an additional basis for the demonstration of neurovegetative and neuroendocrine mechanisms that have been invoked to explain the etiology and pathogenesis of peptic ulcer. In fact, taking into consideration the close relationships between the two systems, their stimulation would produce, through the vagal and the hypothalamus-hypophysis-edrenogastric pathways, the generating conditions of this disease. Hypersecretion, one of its components, is reflected by the presence of high amounts of uropepsin.

Ulcerous vagotomized patients generally show a slight decrease and, in many cases, no changes at all in their amounts of uropepsin, if therapy is not effective. We should also mention the possibility of a chronic stress condition that maintains, through the neuroendocrine pathway, the ulcerogenic factors, even in the absence of vagal stimulation.

Urinary pepsinogen does not vary with the volume of urine excreted, with its pH or its specific weight. Even in patients with a severe renal injury, retention of urinary pepsinogen does not appear. It is not modified by sleep, insomnia or exercise. It is highly probable that there are not in the urine any uropepsin-inhibitory substances, since it maintains its constant enzymatic activity even for a period of four days under normal temperature conditions or two weeks at 4 degrees C., without the addition of preservatives in both cases. Once acidification has been performed in a convenient form, uropepsin starts to exhibit its proteolytic action in the presence of an adequate substratum. This means that the addition of an acid compound is enough to operate the transformation of uropepsinogen to uropepsin, with a measurable peptic activity.

In certain ways, the process followed by pepsinogen when it is transformed to pepsin in the stomach can be produced artificially.

Clinical Importance

Peptic ulcer:—Uropepsin is frequently measured in this condition. Approximately double amounts than the normal are obtained in duodenal ulcer and in ulcers located near the pylorus. Lesser values are obtained in gastric ulcer. The meaning of these amounts is similar to that of gastric pH.

In patients submitted to surgical operations, the excretion of uropepsin has been studied, and important results have been obtained: vagotomized patients do not show marked alterations, but whenever a concomitant gastrectomy is performed, a decrease proportional to the amount of removed tissue occurs. If, under these conditions, the hypophysoadrenal complex is stimulated, secretion increases considerably. The frequency of relapses is generally accompanied by a return to high uropepsin levels, particularly when there is a development of an anastomotic (marginal) ulcer, or after a useless gastrectomy with jejunostomy.

Operated peptic ulcer patients may show, after a certain time, some symptoms such as epigastric pain, hematemesis or rectal bleeding, which, when appearing together with a high uropepsin excretion, suggest, with many probabilities, the development of a new ulcer. Asymptomatic cases with an increase in uropepsin have been reported, in which there were relapses, proven by x-rays or surgery.

A very important indication for the determination of uropepsin is the bleeding of the upper digestive tract, since a high amount of uropepsin may incline diagnosis to the possibility of an ulcer, as the source of bleeding. Radiologic studies do not show early signs of a great interest and gastric juice examinations may be indicated at times. A study, however, on the amounts of uropepsin, although it may not be considered as a total diagnostic means, should be taken into consideration as an easily performed examination that can furnish a valuable help.

Gastric cancer:—In the presence of an ulcerous gastric injury, a low amount of uropepsin points to the possibility of cancer. Nevertheless, the condition may have a normal uropepsin figure course, or may have uropepsin in the lowest levels. This examination does not have an exclusion value. Here, too, it is comparable to the studies on gastric acidity. Although the uropepsin amounts are generally low in gastric cancer, they never reach the minimal values, which are reserved for those conditions which accompany achilia. Total surgical operations (gastrectomies) bring along the disappearance of the enzyme in urine. Its reappearance, some time after the operation, and its increase, as a response to ACTH stimulation, seems to point to the development of active gastric tissue metastases, according to which, prognosis darkens.

Pernicious anemia:—In this condition, an absence of uropepsin is a feature, being thus useful for differential diagnosis in anemias of different types. Gray found minimal values in only 5 of 70 patients. The rest of them did not show the enzyme. Endoscopy was performed in all cases and it showed an atrophic gastric mucosa whenever the urinalysis was negative. The duration of treatment did not influence pepsinogen excretion. Here, uropepsin excretion has the highest clinical value.

Gastritis:—Chronic gastritis types that are accompanied by hypochlorhydria reduce considerably the uropepsin amounts. In cases of achilia, there is a complete lack of it.

Endocrine conditions:—Those endocrine conditions generated by a glandular deficiency, such as panhypopituitarism, hypothyroidism (myxedema), Addison's disease, etc., show low uropepsin levels. On the contrary, there is an elevation when endocrine diseases are due to hyperfunctioning: Cushing's syndrome, for instance, where there is a marked parallelism between 17-hydroxycorticosteroid, 17-ketosteroid and uropepsin amounts.

With the consideration in mind of a possible alteration in the secretion of uropepsinogen in the course of thyrotoxicosis, it has been shown that there are not enough variations to regard uropepsin as having a given value in the differential diagnosis of this condition. In the same manner, the adrenogenital syndrome does not bring marked changes either, perhaps because gastric activity only shows secondary modifications to those of glucocorticoids.

Actions of ACTH and cortisone:—Their administration markedly modifies the uropepsin amounts, increasing them in an important manner. This increase is produced even after subtotal gastrectomies or vagotomies and even when anticholinergic drugs are used. The increase brought about by ACTH, which is more marked than that of cortisone, is similar to the one produced in the excretion of 17-hydroxycorticosteroids and 17-ketosteroids, keeping a close relationship with their variations. On the basis of these important facts, a possible control of therapy with these hormones has been invoked, particularly in those

cases requiring the administration of high doses during long periods, where there would be a basis for a reduction or suspension of the treatment when the uropepsin levels show the possibility of ulcerations due to an excessive gastric stimulation, since its levels are exceptionally high in these cases.

Practical Applications

Methods used:—We have selected the method that is described below, as being the one that has served as a basis for the studies performed in our country. This method furnishes us the additional possibility of being able to refer the results to the averages found previously here.

1. *Reagents:*

HCl	0.3N
HCl	1.15N
HCl	3.5N
NaOH	0.5N
Trichloroacetic acid	0.3N

Concentrated hemoglobin solution Folin-Cicalteau reagent, composed of:

Sodium tungstate	100gm.
Sodium molibdate	25gm.
Distilled water	700c.c.
Phosphoric acid, 85%	50c.c.
Concentrated HCl	100c.c.

2. *Materials:*—
   Beckmann's potentiometer
   Tubes and tube racks (8 for each determination)
   Small funnels
   Whatman No. 5 filter paper
   Filters
   Volumetric 5 c.c. pipettes
   Pipettes, 10 c.c.
   Colleman Jr. spetrophotometer cell
   Water bath, 37 degrees C.

3. *Principles:*—Hemoglobin, in the substratum, is attacked by uropepsin, undergoing a transformation, from which tyrosine and phenilalanine are liberated, and can be determined colorimetrically through the addition of Folin-Cicalteau's reagent, which changes to blue in the presence of hydroxyl groups in phenolic radicals, such as the ones in these aminoacids. Thus, uropepsin units are indirectly determined in urine, since the determination carried on gives a figure of the present milligrams of tyrosine, in view of the proteolytic degradation caused by uropepsin in the hemoglobin molecule.

4. *Technic:*—Acidity of urine samples should be measured, with the purpose of adding different HCl dilutions, depending on their pH, in order to obtain 1.5, the degree in which there is a maximal uropepsin activity. This degree of acidity is preferred because some investigators have stated that at 3.5 there is also a probable action of cathepsine.

The solution is gauged in order to work with equal volumes.

The hemoglobin substratum is put in two tubes (N and N′), previously acidified, with 1 c.c. of diluted urine.

Tubes marked N are incubated at 37 degrees C. during 30 minutes, the period of time necessary for the enzymatic process. On the contrary, proteolysis is immediately stopped in N′ tubes through the addition of trichloroacetic acid, a suspension that will be carried to N when the necessary time has elapsed.

Both tubes are filtered.

The phenol reagent needs an alkaline medium in order to carry on its action. This is obtained by adding NaOH to the tubes. After this, 3 c.c. of the Folin-Cicalteau reagent is added, allowing it to act during five chronometered minutes.

Under these conditions, the only difference left between tubes N and N′ is incubation in the former. Urine normally contains some aminoacids such as tyrosine. Their presence is not a result of uropepsin activity, because of which it is necessary to measure it, with the purpose of removing this amount to the tyrosine milligrams obtained after the hemoglobin proteolysis caused by uropepsin. Since the N′ tubes are not incubated, they will only show the amounts of tyrosine already present in urine.

The last step is the colorimetric reading of both tubes in the spectrophotometer and the transformation accordingly to the adequate tables, made with the standard tyrosine curve.

5. *Estimations:*—Since urine has been diluted four times, the final reading will represent the milligrams of tyrosine in only .25 c.c. of urine; then, if the amount in 1 c.c. is to be known, it will have to be multiplied by 4.

The peptic unit (P.U.) is "the amount of pepsin that 0.04 mg. of tyrosine can liberate from a hemoglobinic substratum in a 2.5 per cent solution after 30 minutes of incubation in standard experimental conditions". The results are expressed in U.P. empyrically, in order not to use tyrosine milligrams as a measure for peptic activity.

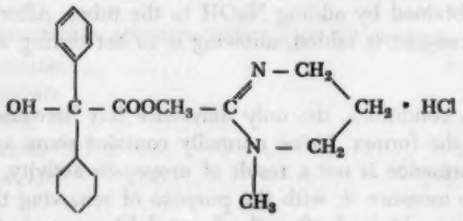
Conversion of tyrosine milligrams to peptic units is done according to the following formula:

U.P.—Tyr. mg. /0.04. This shows U.P. in 1 c.c. of urine. It should be multiplied by the urinary volume of 24 hours, thus obtaining the P.U. of the total volume.

Clinical material:—This study was performed in 50 persons, 7 of which had a diagnosis of peptic ulcer, 5 duodenal and 2 gastric. The rest were apparently normal. Uropepsin was determined in normal conditions; when the amounts were known, the anticholinergic drug was administered and its uropepsin excretion was measured again, this time under its action.

S1–1236 was administered in different dosages: one case, 125 mg.; 22 cases, 50 mg.; 27 cases, 25 mg. The reason for this variation in dosages was to make a comparison of side-effects and the changes that may have occurred in uropepsin quantities by the use of different doses of the drug.

Compound S1–1236:—Chemically, compound S1–1236 is 1–methyl–1, 4, 5, 6, tetrahydro–2–pyrimidyl–methyl–cyclohexyl–phenyl–glycolate HCl, with the following structural formula:



This substance is a white powder, crystalline, hydrosoluble, with a bitter taste.

Toxicity:—Toxic phenomena produced by S1–1236 have been studied as follows:

1. *Acute:*—By the oral or intravenous administration of large quantities of the compound to rats and mice, comparing it with some other anticholinergic compounds.

The figure 1.0 for S1–1236 is arbitrary and was established only for comparative purposes.

Table I thus allows the conclusion that S1-1236 is less toxic by the oral route than the other anticholinergic mentioned and that only atropine sulfate has advantages by the intravenous route, showing a lesser injurious ability, since Banthine, Pamine, Pro-Banthine and Talpran require considerably lower doses to show toxic effects.

2. *Subacute:*—Experiments were performed in dogs, administering doses of 3, 10, 30, 100 and 300 mg. per kilo of body weight each day during six days

of the week. Hemoglobin determinations were made in every case, blood cell counts, bromsulfalein tests, sulphophenolphthalein renal clearance tests, glycemic curves, NPN in blood, and total urinalysis.

A decrease in sulphophenolphthalein clearance was noted, as well as a loss of weight in most of the animals, from the 100 mg./kg. a day dosage up.

TABLE I

	LD 50 mg./Kg.	Relative toxicity
Mice I.V. Route		
S1-1236	80	1.0
Atropine sulfate	64	1.3
Pamine	29	2.8
Banthine	6.8	11.8
Pro-Banthine	6.4	12.5
Talpran	4.2	19.0
Oral Route		
S1-1236	860	1.0
Atropine sulfate	760	1.1
Rats I.V. Route		
Atropine sulfate	122	0.7
S1-1236	88	1.0
Pamine	42.5	2.1
Talpran	6.4	13.8
Banthine	4.8	18.3
Pro-Banthine	4.0	22.0
Oral Route		
S1-1236	1370	1.0
Atropine sulfate	980	1.4

After 5 to 14 administrations of the highest dose (300 mg.) toxic phenomena appeared in all dogs. Nevertheless, various symptoms with all doses administered were observed; mydriasis with a decrease of reflexes to light and, in several cases a formation of white or yellow secretion, lowering of oral and nasal secretions, an elevation of temperature, tachycardia, ophthalmic inflammation, tremor, ataxia, hind leg spasticity and a lowering of motor voluntary activity. Discoloration of the tongue and abdomen may be observed with high doses.

TABLE II

RESULTS

Cases	Age	Sex	Clinical diagnosis	P.U./1,000 c.c. (control)	Oral S1-1236 (mg.)	P.U./1,000 c.c. after administr.
1	23	M	Duod. ulc.	5200	125	2700
2	44	M	Normal	1800	50	1300
3	25	M	"	1720	"	1200
4	23	M	"	1500	"	1250
5	18	F	"	2000	"	1000
6	46	F	"	1700	"	1000
7	44	F	"	2000	"	1200
8	16	F	"	2200	"	1500
9	18	F	"	2100	"	1050
10	19	M	"	1500	"	850
11	23	M	"	1580	"	1300
12	33	M	"	1400	"	1000
13	53	F	"	3000	"	2000
14	30	F	"	4000	"	1000
15	24	F	Duod. ulc.	4800	"	2200
16	55	F	Normal	3050	"	1000
17	27	F	"	2000	"	1200
18	37	M	"	3100	"	2000
19	33	M	"	4500	"	1300
20	42	F	"	3000	"	1800
21	51	M	"	2000	"	1000
22	41	F	"	2100	"	1500
23	34	M	"	1700	25	1000
24	10	F	"	1050	"	700
25	12	F	"	2000	"	1200
26	35	F	"	3000	"	1000
27	24	F	"	2000	"	1200
28	35	M	"	4500	"	1500
29	13	F	"	1000	"	650
30	12	F	"	1500	"	1200

TABLE II *(Continued)*

Cases	Age	Sex	Clinical diagnosis	P.U./1,000 c.c. (control)	Oral S1-1236 (mg.)	P.U./1,000 c.c. after administr.
31	13	F	Normal	2800	25	1000
32	65	F	"	2000	"	1200
33	36	M	Gast. ulc.	4100	"	2800
34	55	F	Healed ulc.	2200	"	1200
35	60	M	Normal	3500	"	1000
36	32	F	"	2700	"	1800
37	18	F	"	2200	"	1500
38	21	F	"	2750	"	1500
39	17	F	"	1000	"	600
40	47	F	"	1000	"	500
41	44	F	"	1000	"	500
42	27	M	"	2750	"	1200
43	18	F	"	1000	"	850
44	16	M	"	1600	"	1200
45	23	M	"	3000	"	2000
46	23	M	"	2100	"	1000
47	52	F	"	1000	"	680
48	30	F	Duod. ulc.	4850	"	1800
49	27	F	Gast. ulc.	4070	"	1800
50	29	F	Duod. ulc.	4900	"	1800

These symptoms appear in less than an hour. Their duration varies with their nature. Mydriasis is probably the longest lasting symptom. It was interesting to note that respiration did not show important changes.

Postmortem findings in some sacrificed animals, as well as in those which had already died, showed degenerative changes in hepatic cells, such as vacuolization or esteathosis of a variable degree. Besides, a hypoplastic thyroid was found in one dog and bone hypoplasia in two.

Anticholinergic and antispasmodic effects:—Atropine, *in vitro*, appears to be 2 to 4 times more potent than S1–1236.

In vivo, atropine and S1–1236 (1 mg./Kg.) caused an inhibition of intestinal motility during an hour, approximately. A dose of 8 mg./Kg. of both compounds

maintained an inhibitory effect during more than six hours after oral administration.

The antisecretory activity was measured in rats and dogs. In rats, a dose of 1.6 mg./Kg. of S1–1236 is enough to obtain a 50 per cent inhibition of free HCl secretion. Doses of 2.3 mg./Kg. of atropine, 1.0 mg./Kg. of Pamine and 5.0 mg./Kg. of Pro-Banthine were needed for a similar effect. Preliminary studies were performed in dogs, and it was observed that 1.0 mg./Kg. of S1–1236 produced an inhibition of hydrochloric secretion in an important degree.

When salivation is induced by pilocarpine, inhibition is similarly obtained with the administration of S1–1236 or atropine.

The effects of atropine on the cardiovascular system are also very similar to those obtained with S1–1236.

It has been observed that S1–1236 has also anticonvulsant effects. Experimentation in this field has not been done yet.

Of all the preceding, the conclusion can be drawn that S1–1236 is a compound with anticholinergic, antispasmodic and antisecretory properties. Its action is both central and peripheric. It is active by the oral route and it is characterized by a long-lasting effect after its administration. It possesses a wide margin of safety and offers results similar to those obtained with Banthine or Pro-Banthine, being less toxic than they are.

Comment

Results obtained coincide with figures previously found in Mexico. These were compared with gastric acid studies, confirming the parallelism observed by every author, for which we have not insisted in this particular point in this paper and we have only taken the uropepsin excretion as a means of knowing peptic activity. Table III illustrates normal and pathological findings in studies performed in our country in 1956.

Our results show that all diagnosed patients as duodenal ulcer carriers excreted amounts over 4,500 P.U. Values of about 4,000 P.U. were found in two patients with gastric ulcer. The minimal amount found was 1,000 P.U.

Summing up, values found in persons with no apparent pathology were as seen in Table III.

These amounts are consistent with the majority of figures published by different authors, although we could note slight variations, principally with respect to the maximal limits, which can be attributed, at least in part, to the lack of x-ray examinations of these apparently normal persons, that could confirm the absence of ulcerous conditions. In every case, figures of 4,000 or more appeared exceptionally in only 3 persons regarded as apparently normal.

After the drug was administered, uropepsin determinations show a clear decrease in peptic secretions, in all the samples studied. This lowering was not proportional to the doses used by which we can state that the effect searched for is obtained with 25 mg. almost in the same manner as with 50 mg.

Side-effects produced by the administration of S1–1236 depend on the amount of milligrams taken. In fact, only in one case were 125 mg. administered and side-effects were marked, with a considerable dryness of the mucous membranes. With 50 mg., different unpleasant feelings may occur. In our series, perhaps headache was the most unpleasant symptom. Mucous membrane dryness with this dose is very variable from one person to another. In an effort to establish clearly every variation of this symptom, it was arbitrarily qualified with three circles whenever it was very marked, and accompanied by cough and dysphonia; two circles if it was annoying, but without these accompanying ele-

TABLE III

No. of cases	Limits	Aver.	Typic. deviat.	Error
16 Males	1000 to 4500	2390	2.91	0.72
22 Females	1000 to 4000	2127	3.30	0.73
5 Children	1000 to 2800	1870	3.70	1.33

Percentage of variation quotients

1.21
1.54
1.97,

ments, and one circle when it was only felt, but in no sense annoying. Mucous membrane dryness was the only symptom that we tried to determine, because the rest of them were not significantly constant nor were considerably important. A case with dermatological reaction should be mentioned; it was characterized by small size papules, itching, in the middle of a slightly erythematous zone, in the face and hands.

With 25 mg. in most of the cases, mucous membrane dryness was only felt. In a few patients it was annoying, but in none did it cause greater alterations. The rest of the symptoms were scarcely present and whenever they appeared, they were considerably tolerated.

It seems logical to conclude from the preceding that if with 25 mg. a day doses only eventual side-effects appear, never of important bearing, and a considerable reduction in peptic secretion is obtained, slightly lower than the one achieved with a dose twice higher, there should be no reasons to use this latter dosage, except under very special circumstances requiring them.

It has been previously confirmed that the action of anticholinergic drugs modified the uropepsin excretion (Silver and co-workers). The present paper further confirms this property and points to the value of the quantitative analysis of uropepsin in this type of studies.

Conclusions

1. Uropepsin determination furnishes important information in those conditions that directly or indirectly alter the gastric secretion.

2. The action of drugs that cause variations in peptic secretion is susceptible of being measured with the use of this test.

3. Uropepsin values found in apparently normal persons were: minimal, 1,000 P.U.; maximal, 4,500 P.U.; average, 2,172 P.U.

4. All cases of duodenal ulcer showed amounts of 4,500 P.U. or over.

5. Anticholinergic S1–1236 caused a decrease in P.U. in every case, having a general average of 41 per cent when 50 mg. were administered, and 44 per cent after administering 25 mg. (approximate values).

6. Side-effects are not significant with 25 mg. a day, thus making this, apparently, the dose of choice.

7. Compound S1–1236 showed to be an effective anticholinergic drug by the oral route.

CLINICAL EXPERIENCE WITH PLANT MUCIN IN THE TREATMENT OF PEPTIC ULCER

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One of the factors concerned with the formation of peptic erosions and ulcers is that of the mucin coating of the mucosa. Hollander[1] and Glass[2] have clarified the role of the mucin coating of the gastroduodenal mucosa and its underlying structures as barriers against ulceration. Insufficient secretion of normal mucin during periods of increased acid secretion is believed to be involved in reducing cellular resistance and in the ultimate formation of an ulcer[3,4]. This may be a result of a deficiency in the supply of chemicals for mucin synthesis or in the vitality of the mucosal cells interfering with their ability to synthesize mucin. Normal human mucin is a viscous, adhesive substance highly impervious to destructive chemicals. It is capable of absorbing and inactivating pepsin, and of neutralizing a substantial amount of acid. Chemically, it consists of polysaccharide-protein complexes referred to as mucoproteins and mucoproteoses. The polysaccharide component consists largely of uronic acid aggregates, chiefly glucuronic acid. It has been demonstrated that certain uronic acid-rich polysaccharides can overcome the chemical deficiencies. Based on the observation that depletion of glucuronic acid can lead to the development of ulcers in experimental animals, Kempton and Bodian[5] showed that the administration of mucin and of pectin or hemicelluloses inhibited the formation of ulcers. These substances act by furnishing galacturonic acid for liver detoxication purposes thus sparing the body reserves of glucuronic acid for mucin production.

Guar cellupectinoid is a new colloidal complex of polysaccharides of plant origin composed of guar and cellupectin. It has a marked physical and chemical resemblance to human mucin. Both complexes yield uronic acids upon hydrolysis, chiefly glucuronic and galacturonic acids.

Clinical Trial

Fifty patients with peptic ulcer or related disorders were treated with a preparation containing this new plant mucin. Forty-five were patients in private practice and five were patients of the Out Patient Department of the Gastrointestinal Clinic at Lebanon Hospital. The preparation used was Balvis tablets**, each tablet containing 275 mg. guar cellupectinoid, combined with 80 mg. of aluminum hydroxide gel, 70 mg. of magnesium oxide, and 160 mg. of

*From the Gastrointestinal Clinic of the Out-Patient Department of Lebanon Hospital, Bronx, New York.

**Supplied by G. W. Carnrick Company.

magnesium trisilicate. The dosage uniformly used was 2 tablets, 4 times daily, administered 1 hour after meals and at bedtime. In an attempt to properly evaluate the efficacy of this preparation, no other antacids were used, and anticholinergics were avoided; however, 8 of the 50 patients were given anticholinergics. Other routine measures were used in the treatment of these patients, including moderately bland foods, milk between meals and at bedtime, superficial psychotherapy, and encouragement to solve environmental and personal problems responsible for stress situations. The medication was continued in the dosage of eight tablets daily for approximately 4 months, following which it was reduced to either 4 tablets daily, or only 2 tablets at bedtime. By the end of six months medication was discontinued in all patients. Observation was continued for a period of 12 months at which time this analysis was made.

TABLE I

36 Cases with Peptic Ulcer

	Total No.	Good	Fair	Poor
Uncomplicated duodenal ulcer	23	21*		2
Duodenal ulcer with stenosis	2		2	
Duodenal ulcer with bleeding	2	1	1	
Duodenal ulcer with penetration	1	1		
Duodenal ulcer & hiatus hernia	1	1		
Pyloric canal ulcer	2	2**		
Steroid ulcer	2	2		
Gastric ulcer	3	3***		

*5 cases given anticholinergics.
**1 case given anticholinergics.
***All showed complete healing by x-ray. One given anticholinergics.

Clinical Results

Results were graded as follows:

Good:—When symptoms were promptly relieved and did not recur for 12 months.

Fair:—When symptoms were satisfactorily relieved, but occasional temporary relapses recurred during the 12-month period.

Poor:—When patient was unable to take the medication, or when the patient complained of distress in relation to taking the preparation, or when there was no appreciable clinical response within 1 to 2 weeks of therapy.

Results in Patients with Peptic Ulcer

Thirty-six patients with peptic ulcer were included in this study and the results are tabulated in Table I. The majority of these had uncomplicated duodenal ulcers, and the rest included duodenal ulcer with stenosis, with recent bleeding, with penetration, with hiatus hernia, pyloric canal ulcers, steroid ulcers, and gastric ulcers. The 2 cases with pyloric canal ulcers were re-examined by x-ray after two months of therapy, and it was then discernible that the ulcer niches were at the base of the duodenal bulb rather than in the pyloric canal. In seven patients, anticholinergics were given because of marked pain. Of the 36 patients with peptic ulcer, 31 (86 per cent) had good results, three had fair results, and two had poor results. The latter two patients complained of increased epigastric distress immediately after swallowing the pills.

TABLE II

14 Cases with Other Disorders

	Total No.	Good	Fair	Poor
Hiatus hernia	3	2	1	
Functional hyperacidity	4	2	2*	
Gastritis	2	1**	1	
Prolapsed gastric mucosa	1	1		
Duodenitis	3	2		1
Recurrent pancreatitis	1			1

*1 case given anticholinergics.

**1 case given anticholinergics.

Results in Patients with Other Related Disorders

Fourteen patients who had a variety of other disorders, as listed in Table II, had responses which were not as favorable as those in the group with peptic ulcers. Of these 14 patients, eight (55 per cent) had good results, four had fair results, and two had poor results. Of these two patients with poor results, one had duodenitis and complained of heartburn after taking the pills, and the second was in a state of remission of chronic recurrent pancreatitis and complained of epigastric distress after taking the tablets.

Untoward Responses

Of the 50 patients, four (8 per cent) complained of heartburn or increased epigastric distress after taking the tablets. One patient complained of recovering the tablets whole in the stool, but this was corrected afer it was poined

out that she should drink 4 oz. of water with each 2-tablet dose. One patient developed a rash one week after taking the tablets; this, however, subsequently was shown to be the rash in the prodromal stage of acute hepatitis which she developed.

Conclusion

In this series of 50 cases treated with the preparation containing the new plant mucin it was observed that 96 per cent of the patients with peptic ulcers, and 86 per cent of the patients with other related disorders had favorable results. There were no significant side reactions. The number of patients in this series was not large enough to permit broad generalization; however, the clinical impression was that this preparation compared favorably with that of other methods of therapy.

Summary

1. A deficiency of human mucin is considered to be one of the factors concerned with the development of peptic ulcer disease.

2. A new preparation containing a plant mucin (Balvis tablets) was used in the treatment of 50 patients with peptic ulcer or related disorders.

3. Favorable results were obtained in 96 per cent of the patients with peptic ulcer, and in 86 per cent of the patients with other related disorders.

4. There were no serious untoward responses, but four patients (8 per cent) discontinued taking the tablets because of heartburn or increased distress.

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CLINICAL EVALUATION OF A 3-HYDROXY-PIPERIDINE (CANTIL) IN THE THERAPY OF INTESTINAL DISTURBANCES*

A Double-Blind, Controlled Study

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For over a decade, anticholinergic agents have been found to effectively inhibit the gastric secretory phase and depress motor activity of the human gastrointestinal tract. These postganglionic parasympathetic inhibiting agents have been employed therapeutically for conditions associated with altered colonic function especially intestinal spasm and diarrhea[1-4]. It has often been observed that the incidence of side-effects of these agents in humans is proportionate to their antisecretory effect and increased intraluminal pressure and intestinal motility. It is felt that the ideal oral compound, therefore, necessary to correct intestinal autonomic disturbances should consist of a specific anticholinergic agent which acts consistently and effectively without tolerance and distressing common side reactions.

Intestinal motor activity has been objectively studied in several ways. These include transit times by serial roentgenologic examinations, direct proctosigmoidoscopic colorimetric visualization, determination of the secretion and lysozyme concentration from the surface of the colonic mucosa, physiological evaluation of exposed intestinal segments, and balloon-intubation-kymographic technics for studying motor activity and direct intestinal intraluminal pressure[4-8]. The shortcomings of these methods have become particularly apparent in studies of intestinal action[4]. On the other hand, an informative and reliable subjective technic to evaluate the clinical effect of a drug in gastrointestinal disorders has been a prolonged, double-blind controlled appraisal in which the factor of therapeutic suggestion is minimized.

The purpose of this investigation was to evaluate the response of an autonomic blocking agent, N-methyl-3-piperidyl-diphenylglycolate methobromide (Cantil) in the medical management of certain intestinal disturbances, particularly those associated with diarrhea. It has been found to be nontoxic and to exert a relatively more depressive response on intestinal physiological preparations than in inhibiting pilocarpine-induced salivation or B-methacholine-induced lacrimation in experimental animals[9]. This agent has been observed to

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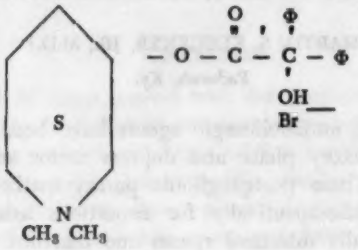
effectively depress colonic motility in humans and produce only a small number of side-effects in previous uncontrolled studies of patients, most of whom had an irritable bowel syndrome[10-12].



Material and Method

The long-term effectiveness of Cantil, atropine and a placebo were compared in three groups of ambulatory patients with various intestinal disturbances. The majority of these cases represented the irritable bowel syndrome or idiopathic chronic ulcerative colitis. The therapeutic effects of these agents were scored particularly by the extent of relief of three abdominal complaints, namely, abdominal pain, abnormal bowel action, and gaseous distress. Complete relief of symptoms was graded 3, if all symptoms were relieved, moderate relief 2, if two symptoms were relieved, minimal relief 1, if only one symptom was relieved and no relief 0 for complete ineffectiveness. The first group observed with intestinal disorders were 28 patients who were prescribed Cantil without a controlled evaluation. The second and third groups were studied by a prolonged, double-blind, controlled trial employing 1. a placebo (lactose); 2. atropine sulfate, 0.6 mg.; 3. Cantil, 25 mg. These agents were supplied by the manufacturer for oral administration in a form indistinguishable to the patient and the examiner, and were prescribed as a capsule an hour before mealtime and at bedtime for four weeks each in randomly assigned order. The second group consisted of 51 patients selected from private practice and a gastroenterology clinic. The third group were 12 patients, evaluated in a psychiatric clinic. All patients were prescribed a bland, low residue diet containing 2,240 calories, 85 gm. protein, 195 gm. carbohydrate and 125 gm. fat. The patients with established chronic ulcerative colitis were also prescribed alternate biweekly doses of salicylozosulfapyridine (Azulfidin) in an average dose of 6 gm. daily in divided doses. In a previous double-blind controlled investigation, salazosulfapyridine was observed to be efficacious in the treatment of idiopathic chronic ulcerative colitis[13]. In addition, a few patients with intestinal parasitic infestations and nontropical sprue were treated in the accepted conventional manner. Occasionally when necessary, sedation was prescribed at bedtime. The three groups of patients were observed by the same examiner for a period of one year and each patient was clinically evaluated biweekly. A physical exami-

nation, complete blood count, urinalysis, proctosimoidoscopic examination, roentgenograms of chest, gallbladder, gastrointestinal tract and colon, stool examination for blood, parasites and ova and bacteriological culture of the stool were performed routinely on every patient. A basal secretory gastric analysis and serial roentgenograms of the small intestine and colon were compared both before and after the oral administration of these agents in certain selected patients.

Results

Group I. Uncontrolled evaluation of Cantil: This agent was markedly effective in relieving abdominal complaints in patients with various intestinal disturbances (Table I). Particularly impressive was the restored bowel habit of

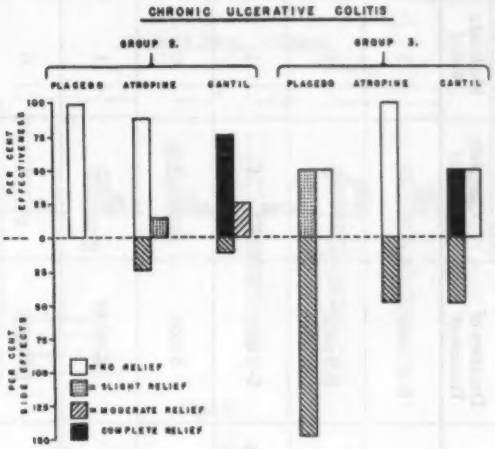


Fig. 1

patients with the irritable bowel syndrome or chronic ulcerative colitis. When the dosage of Cantil was properly individualized, side-effects were minimal.

Group II. Controlled evaluation of Cantil, atropine and a placebo:—This study of patients observed in private practice and a gastroenterology clinic disclosed the superior therapeutic effectiveness of Cantil over atropine, and atropine over the placebo in the management of intestinal disturbances. On the other hand, the incidence of side-effects of atropine were greater than Cantil (Fig. 1). In no instance were the side-effects of any agent severe.

Group III. Controlled evaluation of Cantil, atropine and a placebo:—The therapeutic results of this study were statistically inconclusive because of the small number of patients observed with intestinal disturbances (Table III).

TABLE I

GROUP I. UNCONTROLLED EVALUATION OF CANTIL IN PATIENTS WITH INTESTINAL DISORDERS OBSERVED IN PRIVATE PRACTICE AND GASTROENTEROLOGY CLINIC

28 Patients	Diagnosis	Dosage of Cantil	Duration of Treatment	Number of Patients				
				Therapeutic Effect				Side-Effects
				Complete Relief	Moderate Relief	Slight Relief	No Relief	
15	Irritable bowel syndrome	25 mg. 1 hr. ac and 25–50 mg. hs	8–12 mos.	13	2	0	0	urinary dribbling (1) dry mouth (2)
6	Chronic ulcerative colitis	25–50 mg. 1 hr. ac & 50 mg. hs	8–9 mos.	3	1	1	1	dry mouth (1) blurred vision (1)
2	Diarrhea from iliac stoma	25 mg. 1 hr. ac & 25–50 mg. hs	5–6 mos.	1	1	0	0	none
1	Recurrent regional ileitis	25 mg. 1 hr. ac & at hs	8 mos.	1	0	0	0	none
1	Bacillary dysentery	25–50 mg. 1 hr. ac & at hs	2 weeks	0	1	0	0	none
1	Massive intestinal resection	25 mg. 1 hr. ac & 50 mg. hs	7 mos.	1	0	0	0	dry mouth (1)
1	Gastrojejunocolic fistula	25 mg. 1 hr. ac & at hs	1 week	0	0	0	1	none
1	Non-tropical sprue	25 mg. 1 hr. ac & at hs	4 mos.	0	1	0	0	none
				19(67.9%)	6(21.4%)	2(7.1%)	1(3.6%)	6(7.1%)

Nevertheless, not only was it difficult to differentiate between the comparative efficacy of the three agents, but the incidence of side-effects exceeded those in group II (Fig. 2). This group disclosed symptomatic benefit of inappropriate constitutional side-effects as a result of treatment with a placebo.

Comment

A double-blind, controlled investigation disclosed that a 3-hydroxy-piperidine, Cantil, was a more effective anticholinergic agent in humans as compared with atropine or a placebo in relieving abnormal bowel action, particularly diarrhea, abdominal pain and gaseous distress in various intestinal disturbances, especially the irritable bowel syndrome and idiopathic chronic ulcerative colitis. When compared with the therapeutic results obtained with atropine or a placebo, side-effects of Cantil were slight consisting of urinary dribbling and

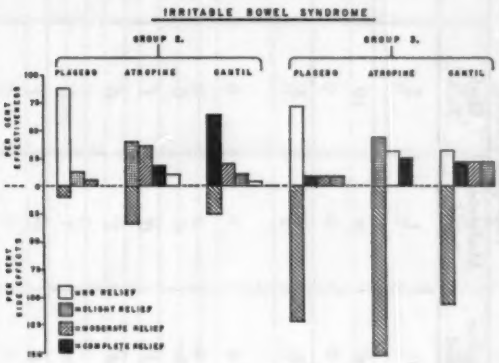


Fig. 2

hesitancy especially in older patients and occasionally dry mouth and blurred vision. This study also disclosed that the gastric antisecretory property of Cantil was invariably slight when evaluated by basal secretory gastric analysis. Motility transit studies of the gastrointestinal tract and colon, determined by serial roentgenograms and balloon-kymographic studies have demonstrated this agent predominantly inhibits motor activity of the colon. Similar clinical and pharmacological studies have also demonstrated the efficacy of other anticholinergic agents in establishing intestinal motor balance, but the appreciable incidence of distressing side-effects frequently impairs their therapeutic use.

The physiological mechanism of Cantil in the relief of intestinal symptoms in various conditions is conjectural. Because this agent appears to be clinically more effective in altering intestinal motor activity rather than having an effective gastric antisecretory effect, it may be postulated that this drug induces a medical pelvic neurectomy by chemically blocking the parasympathetic motor

TABLE II

GROUP II. CONTROLLED EVALUATION OF CANTIL IN PATIENTS WITH INTESTINAL DISORDERS OBSERVED IN PRIVATE PRACTICE AND GASTROENTEROLOGY CLINIC

			Number of Patients				
			Therapeutic Effect				Side-effects
51 Pts.	Diagnosis	Drug	Complete Relief	Moderate Relief	Slight Relief	No Relief	
27	Irritable bowel syndrome	placebo	0	1	2	24	weakness (1); nausea (1); indigestion (1)
		atropine	5	9	10	3	dry mouth (5); blurred vision (4)
		Cantil	18	5	3	1	dry mouth (3); blurred vision (1); urine dribbling (1); fatigue (1)
8	Chronic ulcerative colitis	placebo	0	0	0	8	none
		atropine	0	0	1	7	dry mouth (2)
		Cantil	6	2	0	0	dry mouth (1)
7	Nonspecific infectious entero-colitis	placebo	0	0	0	7	none
		atropine	4	2	1	0	dry mouth (1); blurred vision (1)
		Cantil	7	0	0	0	none
3	Antibiotic entero-colitis	placebo	0	0	0	0	none
		atropine	0	0	1	2	none
		Cantil	2	1	0	0	none

1	Blind-loop syndrome with diarrhea	placebo	0	0	0	1	none
		atropine	0	0	1	0	none
		Cantil	1	0	0	0	none
1	Recurrent regional enteritis	placebo	0	0	0	1	none
		atropine	0	0	1	0	dry mouth (1)
		Cantil	1	0	0	0	none
1	Chronic intestinal amebiasis	placebo	0	0	0	1	none
		atropine	0	0	0	1	none
		Cantil	0	0	1	0	none
1	Ileosigmoid-ostomy	placebo	0	0	0	1	none
		atropine	0	0	0	1	dry mouth and blurred vision (1)
		Cantil	0	1	0	0	none
1	Chronic sigmoid diverticu-litis	placebo	0	0	0	1	none
		atropine	0	0	1	0	dry mouth (1)
		Cantil	1	0	0	0	none
1	Post-gastrectomy steatorrhea	placebo	0	0	0	1	none
		atropine	0	0	0	1	none
		Cantil	0	0	0	1	none
		placebo	0 (0.0%)	1 (2.0%)	2 (3.9%)	48 (94.1%)	3 (5.9%)
		atropine	9 (17.6%)	11 (21.6%)	16 (31.4%)	15 (29.4%)	16 (31.4%)
		Cantil	36 (70.6%)	9 (17.7%)	4 (7.8%)	2 (3.9%)	7 (13.7%)

innervation of the pelvic colon, probably at the ganglionic level. Along this line, male patients occasionally noted diminished libido and urinary dribbling and hesitancy from therapeutic doses of Cantil.

The symptomatic relief obtained by the administration of a placebo and the unusually high incidence of side-effects when all three agents were prescribed to psychiatric patients with intestinal disturbances demonstrates the difficulty in subjectively evaluating an oral preparation in patients with emotional diseases[14]. The toxicity and therapeutic effect of a placebo as the result of suggestion and conditioning in human subjects has been postulated by several investigators[15-16]. The patients in group III suffered from severe psychoneurosis, in whom reorientation of the personality was the main object of the psychiatric clinic. These patients were generally overconcerned with their health and taking a medicine often became a "sacred action". This deterred the patient from facing an emotional problem and often resulted in an abuse of medication[17]. It was apparent that Cantil was symptomatically more effective in the passive, aggressive anxious rather than the passive, dependent type of psychiatric personality.

It became apparent that Cantil was only a useful adjunctive therapeutic measure in the treatment of intestinal disturbances. The importance of a bland, low residue diet, of a proper sedative, or ataractic agent and nonhabit-forming bulk-laxative, relief of aerophagia, regularity of eating, occupational routine, sleep, rest, physical recreation, vacations, and bowel habit, avoidance of tension, correction of faulty hygienic habits and psychotherapy cannot be overemphasized. Attention to these details may well mean the difference between satisfactory progress and therapeutic failure in intestinal disorders. It is also recognized that the natural clinical history of most intestinal disorders, particularly the irritable bowel syndrome, chronic ulcerative colitis, nontropical sprue and regional enteritis are characterized by symptomatic relapses and remissions. This characteristic feature interferes with therapeutic appraisal of these conditions and is minimized only when an investigation is properly conducted in a controlled manner over a sufficiently prolonged period of time.

This study also disclosed that the daily dosage of Cantil varied and depended upon the body weight and the severity of the intestinal disturbance. The therapeutic dosage varied from 25 mg. twice daily to 50 mg. four times daily. The side-effect of an anticholinergic agent employed therapeutically for a gastrointestinal disorder may be sedation. Consequently, it is recommended that the usual daily dosage of an ataractic or sedative drug be initially reduced when prescribed along with Cantil. It has also been demonstrated that the phenothiazide ataractic agents have an anticholinergic property and that the rauwolfia preparations have a predominantly cholinergic-like effect[18]. Therefore, the dosage of these agents should be modified accordingly when prescribing Cantil.

TABLE III

GROUP III. CONTROLLED EVALUATION OF CANTIL IN PATIENTS WITH INTESTINAL DISORDERS OBSERVED IN A PSYCHIATRIC CLINIC

12 Pts.	Diagnosis	Drug	Number of Patients: Therapeutic Effect: Complete Relief	Moderate Relief	Slight Relief	No Relief	Side-effects
9	Irritable bowel syndrome	placebo	1	1	1	6	weakness(3); dizziness (2); indigestion(2); dry mouth(1); headache (2); myalgia(1)
		atropine	2	0	4	3	weakness(4); dizziness (4); dry mouth(2); headache(2); myalgia (1); anorexia(1)
		Cantil	2	2	2	3	weakness(3); dry mouth (2); headache(2); myalgia(2); blurred vision(1)
2	Chronic ulcerative colitis	placebo	0	0	1	1	nausea(1); headache (1); weakness(1)
		atropine	0	0	0	2	weakness(1)
		Cantil	1	0	0	1	weakness(1)
1	Diabetic diarrhea	placebo	0	0	0	1	none
		atropine	0	0	0	1	none
		Cantil	0	1	0	0	none
		placebo	1 (8.3%)	1 (8.3%)	2 (16.7%)	8 (66.7%)	14 (117%)
		atropine	2 (16.7%)	0 (0.0%)	4 (33.3%)	6 (50.0%)	15 (125%)
		Cantil	3 (25.0%)	3 (25.0%)	2 (16.7%)	4 (33.3%)	11 (91.7%)

Summary and Conclusions

The clinical effectiveness of a new anticholinergic agent, Cantil, an analogue of 3 hydroxy-piperidine was determined in various intestinal disturbances, particularly the irritable bowel syndrome and idiopathic chronic ulcerative colitis by a long-term double-blind, controlled investigation. When evaluated on the basis of relief of abdominal pain, abnormal bowel action, usually diarrhea, and gaseous distress, Cantil was found to be therapeutically more efficacious than atropine or a placebo and to produce few undesirable side-effects. When studied by basal secretory gastric analysis, serial intestinal roentgenograms, and balloon-kymographic technic, this agent was demonstrated to exert marked inhibition of intestinal motor activity and to have a mild gastric antisecretory property. This study was also conducted among patients with intestinal disturbances in a psychiatric clinic. All three agents produced a marked incidence of side-effects and the placebo relieved intestinal complaints. Cantil appeared more effective in passive, aggressive anxiety type of psychoneurosis with intestinal disturbances.

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SEROUS CHOROIDITIS ASSOCIATED WITH AMEBIASIS*

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This will be a report regardling the *Endameba histolytica*, which was first differentiated by Schaudinn from the *Endameba coli* in 1903. The organism itself was first described by Losch in 1875. Particular reference will be made to the ability of the endameba to form metastatic lesions in the choroid of the eye.

Reviewing briefly, it will be recalled that the ameba has been isolated in varying degrees from patients all over the world. Apparently it is more prevalent in tropic and subtropic populations. Its life cycle consists of trophozoites, precysts, metacysts, and metacystic trophozoites. The living trophozoite is capable of locomotion and is usually present in liquid or semiliquid stools. They will be found to contain blood corpuscles and bacteria, but generally they live in the colon utilizing mucous secretion as food and living in symbiosis with the enteric bacteria. With dehydration in the colon the trophozoite may discharge undigested food and enter the precyst stage. With the formation of four nuclei and a thin wall, a cyst occurs. The wall is capable of resisting gastric secretions and will break down in the alkaline secretions of the small intestine to make possible the spread of infection to a new host. The cyst can be carried not only by man himself, but through the means of flies or cockroaches.

In the new host, with the breakdown of the cyst wall, four metacystic trophozoites are now available for infestation in the large intestine and the development of active trophozoites. Another factor for consideration is the necessity for the ameba to find suitable enteric bacteria capable of providing the necessary characteristics of oxygen reduction or other requirements which are apparently needed for the ameba to remain outside the tissue themselves. Although not definitely established, it is possible that some species of *E. histolytica* are more capable of invasion than others. From the primary area of invasion, usually an ulceration of the cecum, ulcers seem to spread throughout the large intestine with the second most frequently involved area to be found in the upper rectum and the lower sigmoid.

In order of frequency, the lesions occurring outside of the intestine will be found in the liver, particularly in the right lobe as noted by de Bakey and Ochsner[1] the pleural-pulmonary area, the brain or the skin. Rarely, there have been reports of involvement of genitals, spleen, adrenals, urinary tract and the pericardium.

*Read before the Mexico Regional Meeting of the American College of Gastroenterology, Mexico, D.F., 27 October 1958.

Our discussion today concerns the development of a lesion in the choroid. Amebiasis is to be considered in the differential diagnosis when it is demonstrated to be present in the stool. The search for a completely dependable antigen for immunologic diagnosis continues. In this case report to be given, the Moan[2] test was utilized.

The Moan test is a precipitin test read as negative or from one to four plus. One and two plus are considered weakly positive and three and four plus strongly positive. This test, according to Moan, is specific even in the presence of negative stools. This test was found to be frequently negative in acute amebic dysentery, but 85-100 per cent positive where tissue invasion had occurred. Five out of five cases of liver abscess were positive. More experience will be necessary to evaluate this test further, particularly as to the time of appearance of the antibody and regarding its persistence after clinical cure.

Case Report

Our patient is a 39-year old white female who was first seen on 13 March, 1956, because of pain in the left lower quadrant. Past history included a hysterectomy for a fibroid uterus in 1953, a ruptured appendix in 1952, and a fissure-in-ano in 1954. At time of her surgery for the fissure in 1954, she was given combiotic, sulfasuxadine and gantrisin. The patient stated that her abdominal pain occurred at intervals of several weeks to months apart and was associated with attacks of diarrhea followed later by constipation. There had been some burning noted with the bowel movement. There were no other associated intestinal symptoms. Review of systems was otherwise completely negative except for urinary frequency, nocturia, once to twice nightly, and some dysuria. There is no previous history of adequate work-up or x-rays in regard to the intestinal tract.

Physical examination, when first seen, revealed an obese white female of the stated age, with the following basic findings: B.P.—140/80, temperature—99.2° orally, weight—212 lbs., height—5 feet 7½ inches. Examination of the head and neck—negative. Fundi appeared to be clear. Thyroid was not enlarged. Heart and lungs—normal findings. Breasts negative for masses. Examination of the abdomen—no enlarged viscera detected. There is slight distention. There is marked tenderness in the left lower quadrant, but no definite masses are felt. There is a healed suprapubic midline incision and a healed right paramedian incision. Pelvic examination disclosed a subtotal hysterectomy. Digital rectal examination was negative.

Urinalysis and I.V.P. were negative. X-rays of the colon showed an extensive diverticulosis particularly in the descending colon and the patient was treated with Tridal and a low residue diet. Patient had two severe recurrences, first in November of 1956 and the second in February of 1957 when she was admitted to the hospital. X-rays disclosed even more extensive involve-

ment of the sigmoid with evidence of diverticulitis and incomplete obstruction. This involved an area of about three inches in length with rather advanced narrowing and distortion of the mucosal pattern. Physical examination was essentially as noted on previous admission. The abdomen now revealed marked distention and the scars as previously noted. No enlarged viscera were detected. There was marked tenderness in the left lower quadrant with a small questionable mass noted. No free fluid could be demonstrated. Peristalsis was active.

Laboratory findings include the following: Hemoglobin 13 gm.; Hematocrit, 40 per cent. WBC 6,800 with normal differential including 4 per cent eosinophils. Platelets were adequate. Bleeding time, 3 minutes. Clotting time, 14 minutes. Urinalysis was negative. VDRL was nonreactive. Chest x-ray was negative. ECG was within normal limits. Stool examination was negative for parasites.

On 14 February, 1957, the patient was prepared with sulfathaladine and neomycin and a colon resection with an end-to-end anastomosis of the transverse colon with the distal sigmoid was done. Postoperatively, the patient received achromycin. Patient was discharged on 23 February, 1957, after a completely uneventful recovery.

Four months after surgery, the patient returned complaining of loss of central vision. This had come on gradually since leaving the hospital in February of 1957. She was referred to Dr. George R. Kolodny, who found the macula of the eye edematous with deep hemorrhages over the fovea. The fovea appeared scooped out simulating a macular hole. The macula of the left eye revealed a hyaline-like deposit in the fovea. The clinical impression was that of central serous choroiditis. Further medical examination including PPD, chest x-rays, blood count, prothrombin time, blood protein studies—were all negative. The sedimentation rate corrected was 20 mm. Following the publication of Bralee[3] and Hamilton's article in July of 1957, the patient was checked for parasites by stool examinations at the M. D. Anderson Hospital and Tumor Institute. On 14, 16, 18 and 20 September, no ova or parasites could be demonstrated on direct examination, culture, or on concentrated specimens. On 11 October a Moan test was reported as three plus. On 24 October the patient was given Diodoquin, three tablets daily for 21 days and the course was repeated after a one-week interval and a recheck of the Moan test 30 December was reported as two plus. On 8 January 1958, the patient was given Aralen—0.5 gm. tablet, four tablets at bedtime for two days, then two each night for 18 days. On 12 February 1958, the Moan test was reported as being one plus. On 19 March 1958, the Moan test was reported as being one plus. On 19 March 1958, the patient was given two tablets at bedtime for 30 days. During this period of time, the activity in the choroid subsided. On 22 May 1958, a Moan test was repeated and surprisingly reported as two plus. The lesion in the eye, meanwhile, has healed.

Comment

A case of a 39-year old white female with choroiditis and negative stools for ameba is reported. A diagnosis of amebiasis was predicated on the finding of a positive Moan precipitin reaction. Further reports will be necessary to determine the value of the Moan test in controlling therapy. A review of some of the characteristics of the ameba is included. One wonders if administration of sulfa drugs and antibiotics with disturbance of the symbiosis with the usual enteric bacteria or the actual resection of the bowel with possible breakdown of normal barriers resulted in the invasion by the *E. histolytica* with involvement of the eye. One more case is added to the nine reported by Bralee and Hamilton in which three were made as presumptive diagnoses. Amebiasis is to be considered in the patient with loss of central vision.

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THE OPERATIVE CHOLANGIOGRAM*

Results of Five Hundred Routine Cholangiographic Studies in Operations on the Gallbladder and the Biliary Tract.

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I have observed rather often that cholecystectomized patients present the the same symptoms as before the operation, or worse. This condition is widely known as the "postcholecystectomy syndrome". In my opinion, this term may give a wrong idea of the problem and could be wrongly interpreted as related to a technical error during the operation or to insufficient exploration, or as indicating cholecystectomy alone was not enough to solve the problem.

In order to obtain better results with this type of operation, the technic has been greatly improved, and when it is done carefully the surgeon can rely

TABLE I

Diagnosis (Preoperative) in 500 Cases

Acute cholecystitis	17
Acute cholecystitis, cholangitis	9
Cholelithiasis	329
Carcinoma of the gallbladder	2
Cholelithiasis, hepatocholedocolithiasis	12
Cholelithiasis, lithiasis of ampulla of Vater	14
Cholelithiasis, carcinoma of ampulla or pancreas	4
Chronic cholecystitis, cholangitis	2
Chronic cholecystitis, pancreatitis	1
Surgical trauma of biliary tract	18
Chronic cholecystitis, nonfunctioning gallbladder	92
Total	500

upon it. Nevertheless the "postcholecystectomy syndrome" can still be present, and this, in most instances, is due to inadequate surgical exploration, e.g., of the head of the pancreas or the surrounding anatomic structures which should be treated, if possible, during the surgical procedure.

The method I consider simplest and the one that carries the lowest percentage of error in operations on the gallbladder and biliary tract is that de-

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scribed by Dr. Pablo L. Mirizzi of Argentina, well known as the operative cholangiographic method.

With this procedure, the surgeon will be sure of the following facts:

a. The anatomic character of the biliary tract in each individual case.

b. The positive or negative signs of choledocolithiasis (very difficult to obtain by other methods.)

c. Pathologic conditions of the sphincter of Oddi.

d. Pathologic conditions of the ampulla of Vater or the head of the pancreas.

TABLE II

OPERATIVE CHOLANGIOGRAM: RESULTS

Normal biliary tract (without surrounding lesions)	232		46.4%
Hepatocholedocolithiasis	38		7.6%
Lithiasis of the ampulla of Vater	29		5.8%
Parasitosis of biliary tract (*Ascaris lumbricoides*)	2		0.4%
Spasm of sphincter of Oddi	34		6.8%
Fibrosis of sphincter of Oddi	19		3.8%
Carcinoma of ampulla of Vater	5		1 %
Cholangitis	30		6 %
Carcinoma of head of pancreas	3		0.6%
Normal biliary tract, pancreatic duct reflux:			
(a) Normal pancreas	71		14.2%
(b) Pancreatitis (biopsy)	8		1.6%
Surgical trauma of biliary tract	18		3.6%
Defective roentgen pictures adequate for diagnosis		19	
Totals	500	19	100 %

e. Pathologic conditions of the surrounding structures involving the biliary tract.

With the postoperative cholangiogram only, these pathologic changes can obviously be detected, but too late.

The operative cholangiogram has been harshly criticized and may be liable to technical errors, as follows:

1. Air bubbles. This may be avoided by flushing first the biliary tract and the mechanism of injection carefully.

The air bubbles change in shape and size and shift about.

2. Extravasation of dye through adjacent periductal structures. Adequate testing of the mechanism of injection plus a correct technic usually enables one to avoid this accident.

3. Too much or too little contrast medium or "moved". With the right equipment, roentgen pictures can be developed very rapidly and repeated if

TABLE III

POSTOPERATIVE DIAGNOSIS

Acute cholecystitis (no calculi), normal biliary tract	16	3.2%
Acute cholecystitis plus lithiasis, normal biliary tract	204	40.8%
Chronic cholecystitis plus lithiasis and carcinoma of gallbladder	7	1.4%
Acute cholecystitis, lithiasis of gallbladder and biliary tract	2	0.4%
Chronic cholecystitis, lithiasis of gallbladder and biliary tract	36	7.2%
Acute cholecystitis, cholelithiasis and lithiasis of ampulla	3	0.6%
Chronic cholecystitis, cholelithiasis and lithiasis of ampulla	26	5.2%
Chronic cholecystitis, cholelithiasis and lithiasis of ampulla, parasitosis of biliary *(ascaris lumbricoides)*	2	0.4%
Chronic cholecystitis, cholelithiasis, spasm of the sphincter of Oddi	34	6.8%
Chronic cholecystitis, cholelithiasis, fibrosis of the sphincter of Oddi	19	3.8%
Chronic cholecystitis, cholelithiasis, carcinoma of ampulla	5	1 %
Chronic cholecystitis, cholelithiasis, carcinoma of pancreas	3	0.6%
Acute cholecystitis, cholangitis	18	3.6%
Chronic cholecystitis, cholelithiasis, cholangitis	12	2.4%
Chronic cholecystitis, cholelithiasis, pancreatic duct reflux (normal pancreas)	71	14.2%
Chronic cholecystitis, cholelithiasis, pancreatitis	13	2.6%
Surgical trauma of biliary tract	18	3.6%
Defective roentgen pictures not adequate for diagnosis (Cholelithiasis, manual exploration of biliary tract)	11	2.2%
Totals	500	100 %

necessary. One does not expect "beautiful pictures" with this procedure, merely to aid us in obtaining the correct diagnosis. In case they are "moved" the anesthesiologist should be forewarned and his cooperation obtained by producing apnea during exposure.

4. Difficulties in differentiation between various types of lesions of the sphincter of Oddi and the ampulla of Vater. Usually, with training, differential diagnosis can be done, nevertheless merely knowing the site of the lesion is of great help.

5. Increase in operating time. When the procedure is first done this disadvantage is probable, but with experience and good cooperation from the roentgen department, the operation usually will take between five and ten minutes.

TABLE IV

SURGICAL TREATMENT OF THE BILIARY TRACT IN RELATION TO INDICATIONS OF OPERATIVE CHOLANGIOGRAM

Opening of the main common duct with operative cholangiographic indications:			139	27.8%
Lithiasis of biliary tract	38	7.6%		
Lithiasis of ampulla	29	5.8%		
Lithiasis and parasitosis (*Ascaris lumbricoides*)	2	0.4%		
Fibrosis of sphincter of Oddi	19	3.8%		
Carcinoma of ampulla	2	0.4%		
Cholangitis	30	6 %		
Carcinoma of pancreas	1	0.2%		
Surgical trauma of biliary tract	18	3.6%		
No opening of the main duct because of operative cholangiographic indications			361	72.2%
Spasm of sphincter of Oddi	34	6.8%		
Reflux of pancreatic duct (without pathology)	71	14.2%		
Pancreatitis	13	2.6%		
Plain dilatation of biliary tract	11	2.2%		
Normal biliary tract	232	46.4%		
Totals			500	100 %

In my own opinion, operative cholangiographic study should be a routine means of obtaining better results, as it has been in the Instituto Mexicano del Seguro Social and private practice, from which 500 cases were reviewed.

SUMMARY

It is shown that the so-called postcholecystectomy syndrome is due basically to faulty surgical technic or to insufficient exploration of the biliary tract. In order to solve this problem a routine operative cholangiogram is recommended.

The most common errors and the way to avoid them are discussed, and the results in 500 cases are presented.

In the author's opinion the taking of an operative cholangiogram is the best exploratory procedure available to surgeons treating the gallbladder and

TABLE V

RELATION BETWEEN CALCULI PALPATED BY MANUAL EXPLORATION OF THE BILIARY TRACT AND CALCULI DEMONSTRATED BY OPERATIVE CHOLANGIOGRAM

Total number of cases	69	100 %
Manual and instrumental exploration	41	59 %
Operative cholangiogram	69	100 %
Percentage of error (Operative cholangiogram)		
Adequate diagnosis	489	97.8%
No diagnosis (defective roentgen pictures)	11	2.2%
Totals	500	100 %

the biliary tract and should be routine if better results are to be obtained. It is easy, simple and quick. There are lesions that could not possibly be diagnosed without it.

Statistics are presented which demonstrate its usefulness.

THE ROLE OF GASTRIC REFLUX IN HEARTBURN AND DISEASES OF THE ESOPHAGUS

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Gastric reflux has received much attention in the past in which clinician, radiologist and surgeon have shared alike. It remained for Albers in 1839 to be the first to record peptic ulcer of the esophagus. This contribution was soon followed by Rokitansky's observation of the presence of acid in the gullet in association with the latter. Experiments performed by Reichmann[1] involving the use of a swallowed sponge yielded consistent evidence of the presence of acid in the esophagus of patients complaining of heartburn. This finding was attributed to the regurgitation of gastric contents, and as further studies of this region were pursued, aided in part by the development of the esophagoscope and x-ray, a more detailed understanding of the area was attained. Before long, it became a matter of general knowledge that inflammation and ulcer of the esophagus was usually limited to its lower half, more particularly in close proximity to the esophagogastric junction. The diaphragmatic pinchcock being normally in a tonic state of closure, the mechanics of gastric flow into the lower esophagus was regarded as being due to relaxation of the musculature surrounding the hiatus. Roentgenologic observations have amply proved these experiences[2]. Infants and children are likewise beset by an incompentency in the physiology of the cardia. In addition, hiatal hernias of considerable magnitude in the latter parallel those found in adults[3]. An analysis of the various factors influencing the behavior of this sphincter-like action has been given much thought. The acuteness of the esophagogastric angle and the degree of diaphragmatic support of the lower end of the swallowing tube, the tone and peristalsis of the stomach and esophagus, intraabdominal pressure[4], belching, hiatus hernia[5], congenitally short esophagus[6], varices of the organ[7] and operative procedures[8] which alter the local anatomic pattern all play their part in this regional disturbance of physiology. Allison[9] has pointed out that where the gullet enters the stomach at an acute angle regurgitation from the latter fails to take place and esophagitis, ulceration and heartburn do not occur. On the other hand, when this acute angle disappears as a result of muscular and ligamental weakness at the cardia, the latter slides up into the mediastinum with a consequent perpendicular suspension of the stomach, to be followed by the upward regurgitation of digestive juices and the development of superficial ulceration and heartburn. Craighead[10] underscores this viewpoint and regards it as the chief offender in the causation of esophagitis. The importance of inflammation of the esophagus is not merely highlighted by its acknowledged prevalence[11] but because of its many pathological and clinical implications. A survey of the inci-

dence of peptic ulcer of the esophagus was reported by Jackson[12]. In 4,000 subjects who were autopsied, he noted the occurrence of 88 patients with peptic esophageal ulcer.

The reflux of gastric juice is not necessarily a constant phenomenon[13], nor can it be asserted that all the factors entering into the etiology of esophageal disease are satisfactorily established. There is still much room for doubt and the pattern of behavior is not universally agreed upon. The pathologist's early description of the changes found at autopsy favored the view of postmortem digestive action on the esophageal mucosa as an explanation of the local findings. Hamperl[14], in 1934, gave the first clear pathologic account of peptic esophagitis as it is known today. As a contributing feature in the cause of this ailment, Fleischner[15] emphasized not only the concentration of gastric juice and the frequency of backflow, but the protective mechanism of the body as well. Its frequent association with duodenal ulcer is regarded as no mere coincidence. In a recent opinion, Wangensteen[16] affirmed the association of heartburn and substernal pain as a sequence to gastric eructation in consonance with the views previously expressed. Flood[17] likewise shares this belief.

Other disturbances which may contribute to the disruption of lower esophageal function include trauma from intubation[18], the presence of aberrant gastric mucosa which may lead to local inflammation, ulceration or obstruction[19], the ingestion of corrosives, scleroderma and nonspecific granuloma simulating regional ileitis[20]. More distant sources likewise produce local effects. Peptic esophagitis with stricture formation in association with disease of the interbrain has been described by various observers[21,22], as well as gastric and esophageal erosions due to a neurogenic basis[23]. Recorded cases of esophagitis have been attributed to pemphigus[24], aureomycin therapy[25], thrombophlebitis within or extraneous to the organ[26], in addition to varied fungus infections[27]. In a critical study of the relationship of the esophagus to heartburn, a series of 48 patients complaining of this symptom were subjected to esophagoscopic examination[28]. Dilute hydrochloric acid was introduced directly in each instance into the lower end of the esophagus. Only five of this number responded affirmatively. The remainder complained of no sensation whatsoever during or after the mucosal application of acid. These observations opened up considerable doubt as to the effect of the reflux of acid and its place in the etiology of heartburn.

Method of Study

A series of patients were selected complaining of heartburn. On the morning of the examination, during the fasting state, the customary Ewald test meal was administered. At the end of 45 minutes extraction of the gastric contents was effected by means of an Ewald gastric tube, and the degree of acidity was assayed. Within a few minutes thereafter, 10 to 15 c.c. of the aforementioned

extractum was reintroduced in its original state through a similar tube which was inserted down to a level of 30 cm. from the upper incisor teeth of the patient, enabling thereby a bathing of the lower esophagus by the patient's own gastric contents. At the completion of this procedure, the patients were queried as to the presence of heartburn or ay other sensation they may have experienced.

At a different sitting the status of the presence of acid in the lower esophagus was explored. While under normal physiologic conditions this would not be anticipated, the consensus of medical thought converges to the concept of a gastric backflow as an etiological factor of esophageal pathology. It is fully appreciated that such a process need not occur constantly or continuously. In furtherance of this investigation, a strip of Congo red paper was firmly attached to the tip of a thick Ewald stomach tube by means of a rubber band. With the patient in a fasting state, the tube was swiftly inserted into the gullet to a distance of 30-35 cm. and withdrawn after a few seconds. A change in color of the test paper was sought for to indicate the presence of acid. The same patient was subjected to a similar procedure but with a different approach. A thin Levin tube with attached Congo red paper was introduced to the same esophageal level. At the outset, a number of subjects were checked fluoroscopically to fix the location of the distal end of the tube. This procedure was eventually discarded as being superfluous. The patient was gently laid on his right side where he remained for a period of 45 minutes to an hour, with head resting comfortably on a pillow and being allayed periodically by a few encouraging words for the purpose of physical and mental appeasement. At the expiration of this time, the tube was withdrawn and color changes of the test vehicle was noted. The same process was repeated on another occasion after the ingestion of a full meal. A most important feature of the patient's role in the undertaking is a detailed ritual embracing the so-called "sermon" to which he was subjected preparatory to the session. It includes a description of what is to be attempted and its duration, with words of comfort—with but one goal—relaxation, without which gagging or retching could not help but vitiate the findings. Flood's experiences add forceful emphasis to the need of this important detail. The patient's complacence is the key to accurate findings. Occasionally and most exceptionally a tense, uncooperative individual would be encountered; and rarely in the midst of the operation, gagging or retching would nullify the procedure. At some future date the routine was duplicated where possible for confirmatory purposes. Here and there the subject would lie in a recumbent position.

A few patients were selected at random and their pharynx and hypopharynx were swabbed with some of their own gastric juice. While a few failed to elicit any sensation to this application, the majority responded with a complaint of burning or sourness, the intensity varying with the degree of acidity and possibly in addition to one's individual sensitivity.

Observations

Peptic ulcer:—Thirty-two patients, in addition to one with pyloric obstruction, one with an associated hiatal hernia, and another with an accompanying cholecystitis were intubated. All of these patients complained of heartburn. Reintroduction of the hyperacid gastric juice into the lower esophagus failed in all of these subjects to reproduce this symptom. The Congo test yielded a color change in but one patient, who was restudied at three different subsequent sessions without duplication of this result. All of the others were negative.

Gastritis:—Heartburn and elevated gastric acidity was prevalent in this series of 31 patients. A sense of burning in the gullet could not be elicited in any upon reinsertion of the juice into the lower esophagus. No Congo color change in this entire group of 31 was obtained.

Prolapse of the gastric mucosa:—All of the six patients had heartburn. A thorough diagnostic survey of the digestive tract revealed but a prolapse of the gastric mucosa. Reintroduction of the gastric meal was followed by a negative response. Three of these were studied by means of the test paper. No local acidity was obtained.

Hiatus hernia:—Gastric hyperacidity existed in each of three patients. The reinsertion and Congo findings were all negative.

Cardiospasm:—Examinations were performed on three patients who complained of heartburn and dysphagia. Esophagoscopy was carried out in each, and no esophagitis, ulceration or stricture formation was revealed. Hyperacidity of the gastric juice was elicited. The symptom of heartburn could not be reproduced by flushing the lower esophagus with the patients' gastric contents. Acidity of the lower gullet could not be established by means of the Congo test.

Benign stricture of the esophagus:—Acid eructation and dysphagia characterized this patient. Roentgen films and direct esophageal visualization established the diagnosis. Etiology was undetermined. A Congo test failed to demonstrate the presence of acid in the region of the stricture which was located at the junction of the lower and middle third of the organ.

Esophageal ulcer:—The terminal end of the gullet, just above the diaphragmatic opening was the seat of roentgenologically and esophagoscopically confirmed ulcer, an aftermath of corticosteroid therapy[29]. The introduction of Congo test paper failed to reveal the presence of acid in this ulcer area.

Allergy:—Diverse allergic manifestations in association with heartburn and gastric hyperacidity appeared in this patient who was esophagoscoped. No local inflammation or pathology was found. Gastric juice applied to the lower esophagus on three separate occasions yielded a definite heartburn response. Two separate Congo tests, however, showed no local acid to account for these findings.

An allergic woman with a marked neurosis complained of heartburn. Esophagoscopy revealed no local disease. Hyperacidity of the gastric contents was obtained. Two gastric juice reinsertions reproduced the symptom of heartburn. A third attempt failed. Again, three separate Congo tests on different days demonstrated an absence of lower esophageal acidity.

A miscellaneous group consisting of four patients with gallstones, one carcinoma of pancreas, four with the diagnosis of neurosis, one with diverticulitis, four with colitis, without any symptoms of heartburn but with high gastric acid had negative reinsertion and Congo findings. Two cases of anacid gastritis (one postgastrectomy) with symptoms of regurgitation and no "sourness" likewise yielded negative results in both tests.

Comment

An appraisal of Lodge's report[30], to the effect that 36 per cent of hospital cases coming to autopsy demonstrated the existence of esophagitis, cannot be readily dismissed nor its clinical implications mitigated. Medical thought has projected this disease as an aftermath of gastric acid and pepsin regurgitation. Equally significant is the evidence adduced which ascribes esophagitis to extraneous sources of origin far removed from this local area.

Surgery has formulated an approach in the management of lower esophageal disease based on the theory of gastric regurgitation. Wangensteen[16] described several patients on whom he performed gastric resection for esophagitis and stricture with satisfying results. He postulates that esophagitis and esophageal stricture may well be the consequence of the acid-peptic digestive mixture paralleling that of duodenal ulcer.

Acid findings of the terminal esophagus, as assessed by means of Congo red studies in a series of patients casts considerable doubt on the total acceptance of this view. That a transitory or occasional leakage of stomach contents into the gullet may take place cannot be gainsaid. It might well occur during belching; but a more sustained or pronounced process would seemingly require an established alteration in function of the hiatal orifice or one based on definite anatomic change of this area. A not unfamiliar experience of intense eructation with a subjective response of sternal burning is by no means unusual. This fleeting complaint does not contravene the acknowledged insensitivity of the intact esophageal mucosa. Propulsion of the regurgitant high up into the oropharynx, which is ordinarily sensitive, may explain this response. To conceive of reflux as a commonly occurring and frequent behavior is untenable when appraised in the light of the Congo test findings. It might be appropriate at this point to underscore the absence of lower esophageal acidity in either of the esophageal ulcer or benign stricture patients recorded. Much emphasis has been directed to this area in explanation of lower esophageal disease. Results of the Congo

test suggest a closer scrutiny of other possible sources of etiology as well. Local trauma inducing alteration of tissue, vascular changes, affections of the nervous system, etc., have proved their role in esophageal pathology. Without doubt, a voluminous discharge of highly corrosive fluid for a sustained period such as occurs in vomiting could cause trouble. An occasional eructation associated with sternal burning or sourness appears to fall short of such action. A positive response to the application of a patient's homologous gastric juice to his oropharynx might serve to explain the incidence of heartburn in which the esophagus itself plays no part.

An over all failure in the reproduction of the symptom of heartburn by direct suffusion of the lower esophagus with the patient's own gastric contents confirms investigations previously conducted[28], wherein it was shown that hydrochloric acid when applied to this region through an esophagoscope likewise failed to elicit a response. The induction of heartburn in the two allergic cases reported in this study, without any apparent local esophageal disease is of more than passing interest. An unusual sensitivity is evidently present in the subjects recorded.

Conclusion

The presumption of gastric reflux as an etiologic factor in lower esophageal disease implies the presence of acid of sufficient amount and concentration to justify its place in diseases of this organ. A diverse series of patients with a presenting symptom of heartburn, in whom titration studies established the presence of gastric hyperacidity, failed for the most part to yield evidence of the existence of acid in the lower gullet. Moreover, the reinstillation of the patient's own gastric juice could not be shown to reproduce the symptom of heartburn of which they complained. Applications of gastric contents to the oropharynx did, however, give rise to a sensation of sourness or burning in many of these subjects. That gastric regurgitation under varied circumstances does take place is indisputable. Its degree and frequency is readily determinable by means of the Congo test method. Theoretic as well as therapeutic considerations invite the establishment of the presence of lower esophageal acidity in a given subject, before its causal relationship to esophageal disease or contemplated medical or surgical procedure can be predicated.

With an intact esophageal mucosa, the symptom of heartburn is an expression of a complaint attributable to an extraneous rather than local esophageal phenomenon.

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TOPICAL ANESTHETIC AND ANTACID IN THE TREATMENT OF PEPTIC ESOPHAGITIS*

A Preliminary Report

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and

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Peptic esophagitis was first described as a clinical entity by Winkelstein in 1935[1] with correlation of the clinical observations and roentgenologic, esophagoscopic, and pathologic data. Heretofore, changes in the mucosa in the lower third of the esophagus had been observed repeatedly at autopsies, but were assumed to be either agonal or postmortem manifestations of no clinical significance.

As the name implies, there is injury to the esophagus the result of regurgitation of gastric contents containing acid and pepsin. Identical lesions, however, which frequently are more severe, have been observed in the lower portion of the esophagus after total gastrectomy when neither hydrochloric acid nor pepsin regurgitation was present. Alkaline intestinal juices containing trypsin could be another cause of "peptic" esophagitis.

There are various contributing factors to this disease. The more frequent are persistent vomiting, as in *hyperemesis gravidarum*, intubation, duodenal ulcer, vagotomy for peptic ulcer, status post-Heller operation for cardiospasm and resection of the cardiac end of the stomach. Hiatus hernia deserves special emphasis as the most frequently associated lesion.

It is believed by some investigators that the presence of misplaced gastric mucosa in the lower portion of the esophagus is an important cause of peptic esophagitis and peptic ulcer of the esophagus. This appears to be questionable as gastric mucosa is almost always present in the lower portion of the esophagus[2]. Moreover, in these islets of gastric mucosa, goblet cells are preponderant, and few acid and chief cells can be seen on microscopic examination.

The incidence of peptic esophagitis has apparently increased during the last decade. The word "apparently" is stressed as we believe the increase is not factual, but is dependent on greater awareness of the condition. The improvement in diagnostic acumen is the result of more careful fluoroscopic and roent-

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genologic observations of the esophagus, and more frequent esophagoscopies and esophageal biopsies. As a result, there are recent reports of large series of peptic esophagitis[3,4].

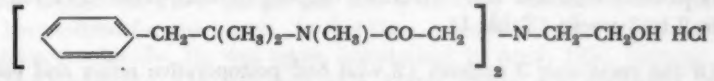
The diagnosis of peptic esophagitis in the reported cases was made on the following evidence. A typical history of retrosternal pressure on swallowing food or soon after eating was present in every case. Postprandial heartburn, often with acid regurgitation, was present in almost every instance. It was aggravated by overloading, eating excessively hot or cold foods and by lying down. Only in the severest cases of long-standing, however, was there an appreciable weight loss. In long-standing cases dysphagia may develop. Strictures in the lower esophagus may also form.

On roentgen-ray examination distortion of the mucosa of the lower esophagus was present in every case. In some patients there was moderate degree of delay in the lower esophagus and some changes in the normal pattern of peristalsis. In five patients gastroesophageal regurgitation could be demonstrated roentgenologically by appropriate maneuvers. Very likely some others may have had it at least at some time. In those cases in which esophagoscopy was performed the diagnosis of esophagitis was confirmed.

During the last 16 months, we have had 13 patients with peptic esophagitis who failed to get relief from symptoms by routine management. One patient in this group had received also roentgen therapy to reduce gastric acidity. Routine therapy for these patients included a bland diet; frequent feedings without overloading; avoidance of excessively hot or cold foods; interdiction of tight belts or girdles; avoidance of bending, stooping, or straining whenever possible; and elevation of the head of the bed. The medications prescribed, either singly or in combination for various periods of time, included aluminum hydroxide gel, aluminum hydroxide gel with magnesium hydroxide, atropine, belladonna, or synthetic antispasmodics. Barbiturates or ataractic agents were prescribed as needed. Neither significant amelioration of symptoms nor improvement in the demonstrable changes in the esophageal mucosa had been obtained. Therefore, a new pharmaceutical agent for the symptomatic treatment of patients with this disease was tried.

Aluminum Hydroxide Gel and Oxethazaine Hydrochloride

Oxethazaine hydrochloride is a new potent local anesthetic for application to mucous membranes. The structural formula of the compound is as follows.



N,N-bis(N-methyl-N-phenyl-t-butyl-acetamido)-beta-hydroxyethylamine hydrochloride

The results of laboratory studies indicate that the compound has a higher potency than cocaine hydrochloride and lidocaine hydrochloride. In experimental animals, oxethazaine hydrochloride shows anesthetic and spasmolytic activity. On topical application or oral administration in experimental animals, there is a very high margin of safety. With large intravenous doses, there is a decrease in blood pressure of a very short duration. There are no toxic effects on oral administration in the doses used by us. The preparation contains oxethazaine hydrochloride as a 0.2 per cent solution. It is stable and not precipitated in an aluminum hydroxide solution. It has been used clinically in the treatment of gastritis[5] and the hyperactive gastrocolic reflex[6].

Method

There were 13 ambulatory outpatients, 8 men and 5 women from 42 to 67 years of age. All the patients had failed to obtain relief from alkalis with or without anticholinergics, ataraxics, or barbiturates. Of the 13 patients, 10 had primary esophagitis; 2 had esophagitis which developed after surgical intervention for gastric conditions; and one had 2 esophageal ulcers. The predominant contributory factor was a hiatus hernia; of the 10 patients, 8 had a hiatus hernia and 4 also had a duodenal ulcer; 2 patients had a diverticulum of the lower portion of the esophagus, alone in one and concomitant with a hiatus hernia in the other; and 5 patients had a demonstrable reflux, alone in one and concomitant with a hiatus hernia in 3. Only one patient did not have any demonstrable predisposing factors. It must be pointed out that a small hiatus hernia as well as an esophageal reflux may easily be missed on routine roentgen examination of the upper digestive tract.

Two teaspoonfuls (8 c.c.) of the aluminum hydroxide gel suspension and 0.2 per cent oxethazaine hydrochloride combination were given routinely after meals. Within one week, the dosage was increased to one tablespoonful (15 c.c.) if the symptoms persisted. In a few instances, 2 teaspoonfuls were given before as well as after meals. The medication was discontinued after the third week unless there was marked improvement. The patients who had satisfactory improvement continued the medication.

Results

Of the 10 patients who had uncomplicated esophagitis, 4 obtained complete relief from their symptoms, and 3 obtained significant amelioration of their symptoms. Three patients failed to respond to the medication. Thus, 70 per cent of the patients who had had intractable esophagitis were relieved or improved within 2 to 3 weeks (Table I).

Of the remaining 3 patients (2 who had postoperative reflux and esophagitis and one who had 2 esophageal ulcers), 2 obtained complete relief from

their symptoms. The patient who previously had a total gastrectomy did not improve.

Except for aggravation of symptoms in the patient who had posttotal gastrectomy esophagitis, no untoward effects were observed.

Report of Cases

The following case histories are typical examples attained by the patients.

TABLE I

Resume of Cases

Cases	Sex	Age	H. H.	Esoph.	Re.	Results
1 M. M.	M	61	+	+ D.	0	good
2 R. S.	F	59	0	+	0	good
3 A. K.	M	64	0	+ D.	0	poor
4 N. B.	M	54	+	+ D. U.	+	good
5 D. M.	M	54	+	+ D. U.	0	partial
6 E. S.	F	67	+	+	0	poor
7 D. H.	F	64	+	+	+	partial
8 F. J.	F	62	+	+	0	partial
9 S. G.	M	42	0	+ St. R.	0	good
10 L. L.	M	67	+	+ D. U.	+	poor
11 I. C.	M	63	+	+ D. U.	+	partial
12 R. L.	F	46	0	Ulcers	0	good
13 M. S.	M	67	+	Gas	+	poor

Gas: total gastrectomy, H. H.: hiatus hernia, D.: diverticulum of esophagus, D. U.: duodenal ulcer, St. R.: stomach resection, Re.: esophageal reflux.

Case 1:—M. M., a man 61 years of age, complained of persistent heartburn for more than 25 years. It occurred 2 to 3 hours after meals, was relieved by alkalis, but not by food. Roentgenologic examination of the gastrointestinal tract did not reveal any evidence of an ulcer or other organic disease.

In September, 1954, the patient had a coronary thrombosis for which he was hospitalized for one month. At that time, a hiatus hernia was demonstrated roentgenographically. He was again hospitalized in April, 1956, because of increasing dysphagia. The presence of a hiatus hernia was confirmed and an esophagitis demonstrated by means of roentgenograms.

Despite the usual management of peptic esophagitis, the patient did not improve. Moderate angina pectoris developed, and the patient retired in January, 1957. Because of persistent symptoms referrable to the esophagitis, aluminum hydroxide gel suspension with oxethazaine hydrochloride, 8 c.c. three times daily, was prescribed. The results were very satisfactory.

In March, 1957, a roentgenogram was taken which showed a questionable esophagitis and a small diverticulum in the lower esophagus, as well as the hiatus hernia.

Case 9:—S. G., male, age 42, was operated upon in May, 1956, for repeated episodes of melena and hematemesis caused by leiomyoma of the upper end of the stomach. In April, 1958, he developed epigastric distress immediately after meals, belching and heartburn. An upper gastrointestinal series revealed a slightly dilated lower end of esophagus with some irregularity of outline in the subdiaphragmatic portion. The stomach and duodenum were normal. On an ulcer diet and alkalis there was some improvement but when oxethazaine hydrochloride was given the patient became asymptomatic within a few days and remained so for nearly two months.

Case 11:—I. C., male, age 63, was carefully observed since 1952, at which time a duodenal ulcer was demonstrated by x-rays. There was good immediate response to ambulatory treatment. One year later his burning and pain became retrosternal. In November, 1954, a hiatus hernia and esophageal reflux were noted. There was only partial relief from a rigid ulcer regime. Esophagoscopy in 1955, revealed an esophagitis of the distal third. Because of failure of routine treatment he received two courses of x-ray therapy to the stomach in July and December, 1956. Total dose was 1.800r. Following it there was a short lived amelioration of symptoms. When symptoms recurred he was placed on oxethazaine hydrochloride with some relief from 1 to 1½ hours. He took the medication irregularly and sporadically. All told, he was distressed almost continually since 1956. Oxethazaine hydrochloride produced the most relief of the many regimes tried in this patient.

Conclusions

In general, the medical treatment of peptic esophagitis is unsatisfactory. Thirteen patients who had intractable esophagitis were treated with a combination of aluminum hydroxide gel suspension and oxethazaine hydrochloride. The results were satisfactory for 9 of the 13 patients (69 per cent). Five patients obtained complete relief from symptoms, and 4 patients obtained amelioration of symptoms. Four patients failed to respond to therapy. Further trial of topical anesthetic therapy in esophagitis is warranted.

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ACUTE PANCREATITIS—CLINICAL STUDY

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Toronto, Ont.

Acute pancreatitis is a frightening disease. It frightens the patient, the physician and the surgeon. Because the individual experiences of any one physician is limited in this disease, I reviewed the patients admitted to New Mount Sinai Hospital for the past three consecutive years. These patients were admitted with a diagnosis of acute pancreatitis. The patients were admitted on both medical and surgical services.

In the three-year study, there were 40 patients admitted with this diagnosis. The diagnosis was either changed or discarded in 19 patients. Twenty-one patients presented satisfactory evidence to be included in this series. The criteria for acceptance in this study were: a history suggesting pancreatitis *and* a serum amylase of at least four times normal in first 48 hours; or proof at operation that acute pancreatitis exists. This does not mean that the diagnoses in the 19 patients were wrong, but being questionable, they were discarded.

In what follows, I shall discuss in brief the problem of pancreatitis as it presented itself to various members of our staff.

All patients were admitted as emergencies. Acute abdominal pain was the outstanding symptom. The diagnoses in all patients later proved to be acute pancreatitis.

TABLE I

VARIOUS ADMITTING DIAGNOSES

Ruptured peptic ulcer.	Acute intestinal obstruction.
Gallstones.	Coronary artery disease.
Acute duodenal ulcer.	Acute pancreatitis.
Acute gastric ulcer.	Carcinoma of head of pancreas.

From the list of various diagnoses in Table I, it becomes evident that acute pancreatitis mimics many serious conditions.

Of 21 patients with acute pancreatitis, 11 or more than 50 per cent were explored surgically and the findings were as follows:

Case 1:—Female, age 19, head of pancreas swollen and enlarged, no other pathology.

Case 2:—Male, age 27, edema of pancreas, no other pathology.

Case 3:—Female, age 64, mass in pancreas, pancreatitis.

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Case 4:—Female, age 41, acute pancreatitis and gallbladder disease.

Case 5:—Male, age 64, pancreatitis and gallbladder disease.

Case 6:—Male, age 57, pancreatitis, no other pathology.

Case 7:—Female, age 34, pancreatitis and gallstones.

Case 8:—Male, age 62, pancreatitis and distended gallbladder.

Case 9:—Male, age 70, pancreatitis and stone in common bile duct.

Case 10:—Male, age 61, pancreatitis, no other pathology.

Case 11:—Female, age 65, pancreatitis, no other pathology.

It is noteworthy that 40 per cent of the operated cases had biliary tract pathology in addition to pancreatitis.

TABLE II

Loss of weight	100%
Pancreatithiasis	37%
Pancreatic cyst	35%
Alcohol abuse	27%
Elevated serum amylase	27%
Diabetes	23%
Narcotic addiction	19%
Jaundice	18%
Associated duodenal ulcer	15%
Pancreatic deficiency	14%

In the reviewed patients admitted with acute abdominal pain and where a diagnosis of acute pancreatitis was substantiated, pain in the upper abdomen radiating to the back and left flank was noted. This pain was very severe and not easily relieved. Most patients required two or more doses of 100 mg. of Demerol. All patients were nauseated and vomited. Abdominal distention was an outstanding feature. Ileus and severe constipation was present. The serum amylase was four times normal (normal 8-32) or higher in the first 48 hours. The pain and other symptoms were so severe, necessitating hospitalization. There was deep tenderness in the upper abdomen. A low grade fever and a definite rise in W.B.C. was present. Flat plate of the abdomen disclosed an ileus.

Nearly all cases responded to Demerol, Levin tube, intravenous fluids, Pro-Banthine, and antibiotics. Little fluid by mouth was given.

Day-by-day appraisal of symptoms was found necessary in order to change treatment or advise surgery. The decision whether and when to operate was most difficult to make both for the physician and surgeon.

One of the most characteristic, and in my opinion the most important finding in the entire series, was a sudden onset of severe acute abdominal pain, sufficient to admit the patient to the hospital. The very acute illness of the patient, was far out of proportion to the findings on physical examination, which were minimal.

The clinical features of chronic relapsing pancreatitis as seen in other studies are shown in Table II.

Summary

In the analysis of cases at Mount Sinai Hospital, acute pancreatitis had a sudden onset with severe abdominal pain; some shock, distention, vomiting, elevated fever and W.B.C.; no definite or specific abdominal physical findings. Previous history of gallbladder disease was present in 40 per cent; history of alcoholism in 20 per cent. Five per cent of cases gave a history of acute attacks following excess of alcoholic intake. The serum amylase was raised 4 times above normal or more in the first 48 hours. X-ray showed ileus.

This represents an over all picture of acute pancreatitis as it was encountered in the analysis of cases at the Mount Sinai Hospital, Toronto.

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ABSTRACTS FOR GASTROENTEROLOGISTS

GASTROINTESTINAL TRACT

ANTIHISTAMINES AND DIPHENYLHYDANTOIN-INDUCED GINGIVAL HYPERPLASIA: F. C. Sturmer, Jr. New England J. Med. 259:485 (4 Sept.), 1958.

The authors tried to confirm the effectiveness of antihistamines as a form of therapy for the gingival hyperplasia that is frequently found in patients who are being treated with diphenylhydantoin sodium for convulsive disorders. They treated 28 patients with antihistamines. These all had gingival hyperplasia and were being treated for convulsive disorders with diphenylhydantoin. Chlorprophenpyridamine maleate, tripelennamine hydrochloride and diphenhydramine were the antihistamines that were used. Results were evaluated by comparison of color pictures that were taken of the gingivae before the start of drug therapy, and of those taken one day before the drugs were discontinued three months later. No improvement was noted in any patient after a three-month course of therapy.

LOUIS A. ROSENBLUM

THE MECHANISM OF POSTPAROTIDECTOMY GUSTATORY SWEATING (THE AURICULO-TEMPORAL SYNDROME): D. H. Glaister, J. R. Hearnshaw, P. F. Heffron and A. W Peck. Brit. M. J. 5102:942 (18 Oct.), 1958.

Gustatory sweating is sweating occurring during the act of eating food in the distribution of the auriculotemporal nerves following parotidectomy, penetrating parotid wounds and suppurative parotitis. It may be associated with localized flushing but is completely independent from general perspiration. The syndrome may occur immediately or months and years after parotid disease or injury. It persists indefinitely. In order to establish the nervous pathways responsible for this abnormal sweating, two patients with this syndrome were carefully investigated after stimulation by chewing moistened cotton-wool and sucking of acid drops. Anesthetization of mouth did not stop the sweating, however, this occurred after blocking of the auriculotemporal nerve. Intradermal atropine abolished it while acetylcholine stimulated it. The sweating was unaffected by sympathetic but arrested by parasympathetic (otic

ganglion) block. Therefore, it was concluded that gustatory sweating is caused by aberrant parasympathetic salivary nerve fibers which had connected with sympathetic end organs (sweat glands).

H. B. EISENSTADT

PROTEAN MANIFESTATIONS OF HYPERPARATHYROIDISM: Robert N. Headley and C. Glenn Sawyer. North Carolina M. J. 19:478 (Nov.), 1958.

A case of hyperparathyroidism in an elderly Jewish woman was presented, and the facility with which this condition can be overlooked was emphasized. Some of the more important aspects of parathyroid overactivity with special reference to this patient were reviewed. Two rather uncommon associated defects, a gastric ulcer and a metastic thyroid adenoma, were discussed.

JACOB A. RIESE

ESOPHAGUS

EXPERIMENTAL STUDY OF TRACHEAL RECONSTRUCTION (RIB GRAFTING WITH A PEDICLE INTESTINAL TRANSPLANTATION): Rikuhei Sato, Jiro Nakagawa, Hideo Kanki, Syozo Koyama, Saburo Hattori and Masaru Dohi. Kobe J. M. Sc. 4:29 (Mar.), 1958.

The authors report their experiences in the experimental correction of tracheal stenosis. They discuss the failure associated with the operative repair of the trachea when an end-to-end anastomosis is performed. They attribute failure to inadequate supporting force of the grafts, abnormal fibroplasia and cicatricial constriction of the increased connective tissue.

Although rib grafting is a reliable method for supporting force, there were many cases in which tracheal stenosis developed without epithelial lining, absorption of the bone tissue and abnormal fibroplasia. To prevent exposure of the transplanted rib on the tracheal internal surface, which disturbs epithelialization due to infection of the transplanted part and necrosis of the grafts, they have recorded disturbance in epithelization due to infection of the transplanted part and necrosis of the grafts. By using polyethylene tubes and a rib graft many of the complications can be avoided.

BERNARD J. FICARRA

ESOPHAGEAL ATRESIA: Christopher Parish and C. F. A. Cummins. Brit. M. J. 5080:1140 (17 May), 1958.

The literature is reviewed briefly by these British authors. The astounding conclusion is arrived at that congenital atresia of the esophagus occurs once in every 800 births; then some 600 children so afflicted are born every year in the British Isles.

Methods of diagnosis are discussed and use of nasal catheter is recommended because diagnosis can then be readily made. Diagnosis of the rare tracheoesophageal fistula without atresia is difficult; bronchoscopy is indicated. The earlier the diagnosis is made, the greater the chance there is that surgery will be successful. It is a well recognized fact that esophageal atresia is associated with other congenital anomalies.

The authors report a series of 17 cases of atresia—type of anesthetic, instruments used and operative procedure is gone into in great detail. Discussion is given on indication and contraindications for use of gastrostomy. Great care is emphasized in performing the anastomosis described and special nurses are recommended for the first postoperative week.

Everyone agrees the higher the birth weight the lower the mortality rate. Fourteen patients in this series had primary anastomosis with a survival rate of 64 per cent; one case had a gastrostomy; one case was diagnosed at autopsy and one case could not be operated. It is recommended that a special team of surgeons be trained to perform this type of surgery.

ABRAHAM BERNSTEIN

ESOPHAGEAL VARICES ASSOCIATED WITH HIATUS HERNIA IN THE ABSENCE OF PORTAL HYPERTENSION: Eddy D. Palmer. Am. J. M. Sc. 235:677-681 (June), 1958.

Ten cases of esophageal varices associated with hiatus hernia are reported. Nine of the patients had surgical repair of the hiatus hernia. Seven of these nine patients were esophagoscoped five to ten weeks postoperatively and no varices were found. No adequate anatomical explanation for the presence of the varices appears evident. Sufficient gastric constriction to cause such varices would certainly cause retention, etc. Twenty-five per cent of hiatus hernia patients have significant bleeding for which esophagitis, esophageal ulcer, erosive gastritis, and gastric and duodenal ulcer are pointed out as sources of bleeding. The author shows the importance of varices that could be demonstrated only by esophagoscopy. The potentiality of these esophageal varices as a source of bleeding is pointed out.

BERNARD FARFEL

X-RAY FINDINGS IN A CHILD WITH CANDIDA ESOPHAGITIS: Herbert J. Kaufmann. New England J. Med. 258:1143 (5 June), 1958.

With modern therapy such as the broad spectrum antibiotics and cortisone products, Candida infestation is becoming very common. The need for recognition of the transition from carrier state to infection is obvious and this article which points out this additional differential diagnosis is well worthwhile reading and considering.

Andren and Theander had previously pointed out (1956) the roentgen changes of *Candida esophagitis* are those of extreme mural pathology with irregular and ragged outline made up of numerous small indentations and protrusions.

The author reports the first pediatric case and the first American case of a four-year old boy who died after prolonged therapy for a refractory aplastic anemia.

IRVIN DEUTSCH

STOMACH

SOME ASPECTS OF THE PATHOLOGY OF PEPTIC ULCER: R. B. Baird. Central African J. Med. 3:140 (Apr.), 1957.

The bulk of evidence points to the fact that cancer is an uncommon complication of peptic ulcer. Cancer never occurs in the ulcer-bearing part of the duodenum and duodenal ulcers therefore never become neoplastic. Part of the difficulty of assessing the problem arises, of course, from the microscopic differentiation of ulcerating neoplasm and neoplastic ulcer, especially where the cancer is of the scirrhus type.

Two other points indirectly support the arguments: 1. Seventy-five per cent of carcinomatous growths in the stomach occur in the pyloric region, whereas the majority of gastric ulcers occur on the lesser curvature. 2. Baird's work on the association of various diseases with blood groups shows that peptic ulcer is more commonly found in persons with blood group O, and gastric carcinoma in those with blood group A.

As to etiology, three factors stand out: 1. There is apparently some hereditary tendency. 2. Stress, emotional or otherwise, appears to precede a considerable proportion of ulcers. 3. In some cases at least, there appears to be an association with exposure to acid juice.

ARNOLD L. BERGER

RECURRENCE OF HEMORRHAGE FROM MEDICALLY TREATED GASTRIC ULCERS: Irwin M. Arias, Norman Zamcheck, Wendell Thrower. A.M.A. Arch. Int. Med. 101:369 (Feb.), 1958.

The frequency of the recurrence of bleeding from gastric ulcers was checked by re-examination of a group of 43 patients who had their original gastrointestinal hemorrhage 4 to 8 years ago. Only nine of them had been initially advised to undergo

surgery but had refused such therapy. Only three of the entire group had had a recurrence of bleeding. One of them belonged to the nine patients who had refused surgical therapy. About ⅔ of this group had medical supervision during all the years; ⅓ was not seen by a physician. Quite a few took moderate or large quantities of alcohol. Sixty-four per cent of this group had symptoms of recurrence of ulcer other than bleeding. This study had to take into consideration that the majority of the severely bleeding gastric ulcers underwent surgery immediately. It leads, however, to the conclusion that if the bleeding gastric ulcer has once completely subsided, the chance of recurrence of hemorrhage is apparently small.

H. B. EISENSTADT

FIVE-YEAR FOLLOW-UP STUDY OF PATIENTS WITH BLEEDING DUODENAL ULCER WITH AND WITHOUT SURGERY: Robert M. Donaldson, Jr., Juanita Handy and Solomon Papper. New England J. Med. 259:201 (31 July), 1958.

This study includes 136 patients of duodenal ulcer with hemorrhage proven by x-ray, appearance of melena, hematemesis, and a bloody aspirate of gastric contents. These cases were chosen after examination of 1,149 clinical records and followed for from 60 to 126 months with an average of 85 months. There appeared to be no seasonal variation in the recurrent bleeding episodes. All the patients who died of hemorrhage were over 50 years of age. The severity of the bleeding episodes failed to reveal a constant pattern; a mild episode could be followed by a severe episode and visa versa. In those who underwent surgery, the immediate death rate was 1.6 per cent. Twenty per cent of the patients operated on primarily for bleeding had recurrent bleeding episodes. The incidence of bleeding in the patients who had surgery for other reasons was negligible. In the total 136 cases the incidence of death was 5.9 per cent. Death occurred primarily in patients over 50, those with pain continuing after onset of bleeding, and those with a rise in blood urea nitrogen over 100 mg. per cent. Patients who have had two or more hemorrhages are most likely to have recurrent hemorrhage. Recurrent episodes of bleeding may occur over 5 years after gastrectomy. One-third of the patients (47 of 136) with gastrointestinal bleeding escaped the subtotal gastrectomy, recurrent hemorrhage, and death within 5 years of the time they were first observed.

ABE ALPER

SOME ROENTGENOLOGIC CONSIDERATIONS IN PEPTIC ULCERS: E. H. Little and Seymour Ochsner. Mississippi Valley M. J. 80:172 (July), 1958.

The authors give a resumé of the most important x-ray changes in peptic ulcerations established many years ago. Peptic ulcers occur in those parts of the gastrointestinal tract that come in touch with gastric acidity, i.e., the lower esophagus, the stomach, the duodenum and the jejunum after anastomosis. Peptic ulceration of the esophagus appears as persistent spasticity of its lower part with slight irregularity of the mucosal pattern. Chronic ulcer shows a definite crater usually associated with disruption of the normal longitudinal folds and with permanent narrowing. Benign gastric ulcer is most commonly found on the lesser curvature. A collection of barium is noticed in a pocket which lies outside of the confines of the stomach. The mucosal folds radiate to the edge of this crater which is surrounded by a flat flexible wall and often associated by localized muscular spasm and tenderness. Unusual gastric ulcers are those in hiatal hernia, ulceration of the greater curvature and in the pyloric canal. These are difficult to distinguish from cancer. The acute duodenal ulcer shows a niche in the profile view and a constant pocket in the frontal view. Localized tenderness, pyloric and duodenal spasm are associated. Chronic duodenal ulcer produces a permanent deformity of the bulb. Identification of an ulcer crater may be difficult. It is usually situated on the posterior wall. Postbulbar ulcers show either segmental narrowing or a localized crater associated with a narrow section.

H. B. EISENSTADT

NONSPECIFIC GRANULOMATOUS DISEASE OF THE STOMACH: Moshe B. Goldgraber, Joseph B. Kiraner and Howard F. Raskin, AMA Arch. Int. Med. 102:10 (July), 1958.

Postprandial bloating, burning, and pain in the epigastrium, hunger pain, hematemesis, anorexia, and weight loss may be caused by granulomatous infiltrations of the stomach which are difficult to diagnose by x-ray and gastroscopy. Specific granulomas are caused by tuberculosis, syphilis, brucellosis, infectious mononucleosis, cat-scratch fever, actinomycosis, histoplasmosis, Hodgkin's disease, and periarteritis. Nonspecific granulomas are associated with trauma, foreign bodies and the allergic states. Four cases of granulomatous disease of the stomach are described. One represented a part of regional ileitis, the other was an eosinophilic granuloma; two cases remained of an undetermined nature. The diagnosis was clinically suspected by the finding of giant cells in the gastric washings. This diagnosis was verified by biopsy at the time of a surgical exploration.

H. B. Eisenstadt

INTESTINES

BENULOSE—A NEW ADJUNCT IN THE TREATMENT OF FUNCTIONAL BOWEL DISTRESS: Charles W. Hock. J. M. A. Georgia 47:336 (July), 1958.

Benulose is a combination of an anticholinergic (Bentyl) with a modified sodium carboxymethylcellulose and sodium lauryl sulfate, the latter two compounds representing bulk producer and wetting agent respectively. The combination is designed to normalize bowel action with respect to frequency and character of defecation. One tablespoonful three times a day was found to be a useful adjunct in the treatment of 54 of a total of 75 patients suffering from functional bowel distress, and it was helpful in the one patient being treated for ulcerative colitis. Benulose should not be confused with laxative or antidiarrheal preparations as it generally produces soft or formed stools no matter what the consistency was prior to its administration.

Walter Cane

ASSOCIATION OF FUNCTIONING CARCINOID SYNDROME AND SCLERODERMA: Chris J. D. Zarafonetis, Stanley H. Lorber and Stephen M. Hanson. Am. J. M. Sc. 236:1-14 (July), 1958.

The authors report a case of functioning carcinoid tumor associated with scleroderma suggesting the extensive fibrosis reported in this particular case is due to the functioning carcinoid tumor. This may give a clue to the causation of scleroderma and other fibrotic states. A following article will be published suggesting that such fibrotic changes result from a disturbance of the interactions of the monoamine oxidase mechanisms at the tissue level.

Although this case was not diagnosed during the life of the patient, a 42-year old white housewife, the detail of history, examination, and clinical progress is noteworthy. The necropsy findings are given in unusually complete detail.

Bernard Farfel

MALIGNANT TUMORS OF THE JEJUNUM AND ILEUM: Everett B. Coulter. Northwest Med. 57:899 (July), 1958.

Malignant tumors of the small intestines are infrequent and constitute only 3 per cent of all gastrointestinal malignancies. Carcinoma being twice as frequent as sarcoma.

Clinical symptoms are usually vague, and early signs are those of intermittent cramplike pain sometimes accompanied by nausea and vomiting. An early symptom is unexplained anemia.

Physical findings of the disease are few, and a palpable mass is usually found late, this is because the tumor does not occlude the lumen but grows, upward into the mesentery.

Roentgen examination offers a high ratio

of preoperative diagnosis if attention is directed to the small bowel and if the examination is carefully done. A roentgen criteria for diagnosis includes filling defects, ulceration of the mucosa, at the site of the lesion and distention of the bowel, proximal to the lesion. Sixteen cases of small bowel malignancy were collected from a Spokane Hospital, with disappointing results. Physical findings demonstrate a mass in 3 out of 16 cases, and anemia in 10 out of 16 cases. X-ray examinations of the gastrointestinal tract, 14 out of 16 cases, with a positive diagnosis of 3 out of 14. Positive preoperative diagnosis of small bowel tumor was made of five of the cases. Results following surgery are extremely poor. Only three patients lived more than two years.

V. J. GALANTE

CANCER OF COLON MASQUERADING AS TUBO-OVARIAN ABSCESS: Claude C. Craighead. Am. Pract. & Digest. Treat. 9:1089 (July), 1958.

Tubo-ovarian abscess is rarely suspected as arising from erosion of colonic cancer, but this author presents three cases of such abscesses collected over a period of about four years.

A simple diagnosis of abscess was not made, instead extensive studies with barium enema, proctoscopic inspection, biopsy and finally open resection of colon adjacent to the abscess area proved the true pathology.

An exploring finger can uncover two-thirds of all colonic carcinomas, a problem in diagnosis is present when one encounters a tubo-ovarian abscess, but sigmoidoscopy will eliminate or confirm malignancy.

Radiography with barium suspension is desirable for often multiple lesions are in the colon and correct procedure depends upon knowledge of their presence.

J. EDWARD BROWN

OPERATIVE COMPLICATIONS OF ANORECTAL SURGERY: Raymond E. Anderson. Clin. Med. 5:913 (July), 1958.

The author points out ten complications resulting from anorectal surgery. These cause situations which affect either the general well-being of the patient or interfere with the normal function of the anorectal mechanism.

The prevention and treatment of these various complications are discussed. The complications mentioned are: 1. Hemorrhage, 2. Excessive postoperative pain, 3. Infection, 4. Outlet stenosis, 5. Incontinence, 6. Mucocutaneous fistula, 7. Alteration of mucocutaneous junction, 8. Pruritus, 9. Anal ulceration, 10. Fecal impaction.

BERNARD FARFEL

ADENOCARCINOMA OF THE SMALL INTESTINE: Allan E. Gilbert and Robert A. Wise. Am. J. Surg. 96:54 (July), 1958.

Clinically, cases of cancer of the small bowel may be classified into three groups on the basis of symptoms: bleeding or anemic, obstructive and perforative. The majority of patients, however, have a combination of findings, especially in respect to obstruction and anemia. The patient may appear pale and chronically ill; abdominal tenderness is common, and frequently the only complaint. A palpable mass is present in 29 to 40 per cent of cases and is considered a late manifestation of the disease.

Carcinomas of the small intestine behave in a manner similar to malignant tumors of the stomach and colon. They occur more frequently in males than in females and although found in patients in all decades, are more common in those between the ages of 40 and 60 years. In making a diagnosis, a certain sequence of events should arouse suspicion. A patient with a diagnosis of peptic ulcer, chronic cholecystitis, chronic pancreatitis or psychoneurosis, who does not respond to adequate medical management, but continues to have abdominal pain, weakness, weight loss, melena and anemia, or any combination of these find-

ings, should be considered to have a tumor of the small intestine.

As a rule, cancers of the small bowel grow slowly, metastasize first to the regional lymph nodes, and only later to other organs, such as liver, lungs, and bone. With the continued development of new diagnostic technics and surgical procedures, the survival rate for patients with this disease will eventually reach a more satisfactory figure.

CARL J. DEPIZZIO

THROMBOTIC THROMBOCYTOPENIC PURPURA OCCURRING IN THE PUERPERIUM: Harold N. Harrison. A.M.A. Arch. Int. Med. 102:124 (July), 1958.

Thrombotic thrombocytopenic purpura is an uncommon hypersensitivity disease related to the collagen disorders and characterized by multiple hyalin thrombosis in the small vessels supposedly caused by clotting of the platelets. Clinically there is a combination of hemolytic anemia with thrombocytopenic purpura and bizarre mental and neurological symptoms. However, in about 10 per cent of cases the abdominal symptoms predominate with epigastric pain, tenderness and rigidity. There is hyperglycemia, glycosuria and increased serum amylase. These findings together with icterus and hepatomegaly, fever and leucocytosis simulate an acute surgical abdomen. Only careful evaluation of mental and neurological findings and laboratory studies of the blood will prevent laparotomy under those circumstances. The cause of the abdominal syndrome is not exactly known but may be due to pancreatic involvement.

H. B. EISENSTADT

JEJUNAL AND ILEAL DIVERTICULOSIS: Robert E. Lee and Nathaniel Finby. A.M.A. Arch. Int. Med. 102:97 (July), 1958.

This study includes 45 patients with diverticulosis of the small intestines. Single diverticula are usually congenital. Most cases have multiple diverticula, they are acquired and occur on the mesenteric border at the sites of vascular penetration. The greatest number of diverticula is seen in the upper jejunum. Diverticula of the ileum are rare and occur mostly at the terminal ileum. Many symptoms and complaints have been ascribed to the diverticula, however, most cases are asymptomatic and only those that have complications present symptomatology. Such complications are diverticulitis, hemorrhage, formation of concretions, obstruction, perforation, volvulus, intussusception, pneumoperitoneum, macrocytic or hypochromic anemia with or without sprue. Also foreign bodies, worm infestations and various tumors such as fibromas, lipomas, aberrant pancreas, carcinoids, sarcomas, and carcinomas have been found in diverticula. In this group only two cases of clinical importance were found, one had macrocytic anemia, the other a diverticulum superimposed upon a gastroenterostomy mistaken for a jejunal ulcer.

H. B. EISENSTADT

FAMILIAL MEDITERRANEAN FEVER: Harry Heller, Ezra Sohar and Libby Sherf. A.M.A. Arch. Int. Med. 102:50 (July), 1958.

This syndrome has been described as benign paroxysmal peritonitis and as periodic fever. These diagnoses must be rejected because the attacks of peritoneal irritation are only a part of the clinical picture. Furthermore, the febrile episodes do not occur at regular intervals. The name of Familial Mediterranean Fever is suggested by the heredofamilial background of the disease and by its almost exclusive occurrence in persons of Mediterranean stock, especially in Armenians and Mediterranean Jews. Attacks of fever of short duration are necessary for the diagnosis; they occur over the course of many years. In addition, there are painful manifestations from the peritoneum, the pleura, the joint surface and the skin. The cause of the disease is unknown and there is no treatment.

The abdominal pain is usually severe, comes on suddenly, is aggravated by movements, is accompanied by vomiting, distention, board-like rigidity, obstipation, ileus, and rebound tenderness. X-ray examination shows an acute abdomen with fluid levels in the small bowels. This crisis simulates acute surgical abdomen but it lasts only 6-12, rarely up to 24 hours; thereafter, it disappears spontaneously. Similar attacks of pleurisy with small effusions and of single or multiple joint swelling may occur at the same time or at different occasions. All these manifestations are of evanescent character. Also erythematous macules or patches may be observed during the attacks.

Physical examination shows sexual infantilism, and sometimes hepatomegaly and splenomegaly. Abnormal laboratory tests include fast sedimentation rate, increased blood fibrinogen and spherocytosis of the red cells. During the attack there is marked leucocytosis and marked elevation of the sedimentation rate. The course of the disease is extremely prolonged. The prognosis is unfavorable. The terminal episode is characterized by nephrosis and renal insufficiency due to amyloidosis.

H. B. EISENSTADT

EFFECT OF ABDOMINAL OPERATIONS ON TOTAL LUNG CAPACITY AND ITS SUBDIVISIONS: Anthony R. Anscombe and Roger St. J. Buxton. Brit. M. J. 5088:84 (12 July), 1958.

The authors studied a group of 26 male patients which was divided into 3 groups. A control group of 10 patients suffered from no abnormal lung conditions. Group II consisted of 13 patients upon whom abdominal operations were performed. Group III was made up of 3 patients only, each of whom had had an operation of similar severity performed upon an extremity.

It appears that an abdominal operation, especially one in the upper abdomen, is followed by a reduction in the subdivisions of the lung volume, and that similar changes occur postoperatively in subjects with evidence of preexisting lung disease. This effect occurring in a patient whose lung function is already impaired is more likely to cause respiratory insufficiency in the immediate postoperative period. It is suggested that any such patient should have the pulmonary function assessed before operation so that measures may be taken to combat any postoperative anoxia which may arise.

Measurements of the total lung capacity and its subdivisions were made on 26 male patients and it was found that significant reductions occurred in the total lung capacity, inspiratory capacity, expiratory reserve volume, vital capacity, and functional residual capacity after abdominal operations, and these changes were more marked after those on the upper abdomen. The article briefly considers possible causes of these changes.

I. HENRY EINSEL

ROENTGEN DIAGNOSIS OF ACUTE APPENDICITIS: Constantine Soteropoulos and John H. Gilmore. Radiology 71:246 (Aug.), 1958.

In a three-year study of acute appendicitis, the possibility of accurate roentgen diagnosis has been proved, even in cases with vague and nonsuggestive symptoms. The x-ray findings are as follows: 1. Fluid level in the cecum best seen in the decubitus position, occasionally associated with small fluid levels in the terminal ileum. 2. Blurring of the distal portion of the right psoas muscle with secondary homolateral scoliosis of the lumbar spine. 3. Coarsening and edema of the mucosa of the cecum. Thickening of the wall of the cecum. 4. Localized ileus of the loops of the terminal ileum, with thickened septa between the loops of small bowel and the cecum. 5. Diffuse increased density over the region corresponding to the cecum and terminal ileum. 6. Flocculent gas densities in the area of the appendix. 7. Fecaliths of the appendix in the presence of suggestive clinical findings. 8. Widening and shortening of the extraperitoneal fat line. A series of cases has been presented and analyzed. The importance of the decubitus position in the x-ray study of the abdomen is stressed.

FRANZ J. LUST

LIVER AND BILIARY TRACT

HEPATITIS, COLITIS, AND LUPUS MANIFESTATIONS: Nigel Gray, Ian R. Mackay, Leon I. Taft, Sara Weiden and Ian J. Wood. Am. J. Digest. Dis. 3:481-491 (July), 1958.

An analysis has been made of eight cases in which hepatitis and ulcerative colitis occurred together. Of the eight patients, three had chronic hepatitis of uncertain pathogenesis and concurrent ulcerative colitis of varying severity and five others had, in addition, systemic lesions including nephritis, pleurisy, pericarditis, polyarthritis, and thrombocytopenic purpura. Evidence for an autoimmune pathogenesis in these cases included elevated serum gamma globulin levels, positive *L.E.* cell tests in four cases, and positive autoimmune complement fixation reactions in six cases. The authors believe that the occurrence in eight patients of hepatitis and colitis, with probably autoimmune disorders in some of them, is more than fortuitous. In fact, the authors conclude, cases such as theirs may be variants of true systemic *lupus erythematosus*.

WALTER CANE

SO-CALLED PAPILLOMAS OF THE GALLBLADDER: G. Edward Schnug. Am. J. Surg. 96:296 (Aug.), 1958.

During recent years the writers have become interested in lesions of the gallbladder called papillomas by the radiologist. They are small radiolucent intraluminal lesions demonstrable in the noncalculus functioning gallbladder on the cholecystogram. In several instances they have removed such gallbladders. Results obtained with cholecystectomy in relieving the symptoms supposedly associated with the lesions were very disappointing. Kerr and Lendrum in 1936 demonstrated that the majority of cases reported in earlier papers were not true papillomas but were instead a form of localized cholesterosis of the gallbladder.

It is usually not possible to differentiate the various lesions by radiological study. By far the most common lesion found is the cholesterol polyp. The second is the true papilloma found much less frequently than the cholesterol polyp. It may be single or multiple and also is frequently associated with cholelithiasis. The third lesion which on the x-ray gives the picture of so-called papilloma, is the adenoma. It is found less frequently than the cholesterol polyp or the true papilloma. The adenoma is found only in the tip of the fundus of the gallbladder.

Other benign tumors are found in the gallbladder but are not confused with the so-called papilloma on cholecystography. In severe cholecystitis, the gallbladder does not visualize on cholecystography and thus a polypoid lesion is not evident on radiological study.

Four patients were found with so-called papillomas of the gallbladder during the course of performing 252 cholecystectomies. No evidence of malignancy was noted in any of the cases.

A study of the eight reported cases in which associated carcinoma of the gallbladder and papilloma were found is revealing. In a careful analysis of these case reports, there were two cases of carcinoma associated with papillomas, with no evidence that the carcinoma actually arose from a papilloma.

CARL J. DEPRIZIO

NONICTERIC INFECTIOUS HEPATITIS: Dayton T. Kieswetter. Internat. Med. Dig. 73:67 (Aug.), 1958.

The virus of infectious hepatitis is hardy, it survives chlorination as well as boiling of drinking water for 10 minutes. Therefore, one must assume that infectious hepatitis in its anicteric form occurs more frequently than it is diagnosed. Thirty-five per cent of all adults show a positive skin test for this disease probably indicating previous infection. Infectious hepatitis occurs most often during the fall and winter time. It may be confused with grippe, brucellosis and infectious mononucleosis, but most often with psychoneurosis because emotional depression is its outstanding

symptom. Diagnosis can be confirmed only by abnormal liver function tests especially cephalin flocculation and thymol turbidity. The treatment consists of bed rest and high-carbohydrate low-fat diet. Specific therapy is lacking.

H. B. EISENSTADT

PATHOLOGY AND LABORATORY RESEARCH

PRECIPITIN REACTION OF GASTRIC JUICE OF PATIENTS WITH GASTRIC CANCER: Kiyota Oh-Uti et al. Tohoku J. Exper. Med. 67:131 (25 Feb.), 1958.

The presence of specific antigens in the gastric juice of patients with gastric cancer has been demonstrated. The gastric juice of the cancer patient has some specific antigens common with the gastric cancer tissue. The specific antigens found in the gastric juices of the cancer patients were destroyed by heating, freezing, and treating with a weak acid, a strong alkali, and formalin.

Of various fractions obtained by the use of ammonium sulfate, the following three fractions were found to contain specific antigens: the precipitate obtained on half saturation, the supernatant obtained on full saturation, and the precipitate obtained on

full saturation with ammonium sulfate. Of various fractions obtained by dioxane, only the precipitate produced by 46 per cent dioxane showed specific antigenicity. Each of the mucoprotein and the mucoproteose obtained from the gastric juice of the cancer patients showed specific antigenicity.

JOHN E. COX

FREE AMINO ACIDS IN GASTRIC JUICE OF PATIENTS WITH GASTRIC OR DUODENAL ULCER AND GASTRIC CARCINOMA, WITH SPECIAL REFERENCE TO THE CHANGE AFTER OPERATION: Kiyota Oh-Uti and Jun-ichi Awataguchi. Tohoku J. Exper. Med. 67:123 (25 Feb.), 1958.

The free amino acids in the gastric juice of patients with gastric or duodenal ulcer and gastric carcinoma were collected by means of ion exchange resin and examined by paper-chromatographic method.

In the gastric juice of healthy stomachs occurred 11 free amino acids. The degree of occurrence, however, was of the order of moderate positiveness.

The gastric juice in cases of gastric or duodenal ulcer showed a tendency to increase in the number of occurring amino acids, but the degree of strong positiveness occurred in only one case. The rate of occurrence after gastrectomy was nearly the same as before operation, but strong

positiveness disappeared after gastrectomy.

In the gastric juice of gastric carcinoma cases, proline, threonine, and a peptide newly appeared in addition to the amino acids seen in ulcer cases. The degree of occurrence of leucine, valine, alanine, serine and glycine, and glutamic acid was remarkably high. The free amino acids in the remaining stomach after gastrectomy showed, in comparison with those before operation, a pronounced depression in the degree of occurrence; and their state of occurrence became similar to that seen in ulcer cases before operation.

JOHN E. COX

A CONTRIBUTION TO THE MYCOLOGY OF THE MOUTH: E. C. Fox and G. C. Ainsworth. Brit. M. J. 5100:826 (4 Oct.), 1958.

In order to evaluate the importance of fungi in the etiology of oral and dental diseases, scrapings and swabs were obtained from 157 patients with angular cheilosis, gingivostomatitis, *lingua nigra, lingua geographica,* and dental sores and from 188 normal persons. Various fungi especially Candida were obtained in a great number of patients as well as normal controls. However, only angular cheilosis and gingivostomatitis exceeded the controls significantly in positive cultures of *Candida albicans,* leading to the conclusion that they might be etiologically significant. All other oral and dental disorders showed the same percentage of positive fungus cultures as the normal. Particularly interesting is the low yield of fungus growth in *lingua nigra,* which is apparently a dyskeratosis and not a fungus disorder.

H. B. EISENSTADT

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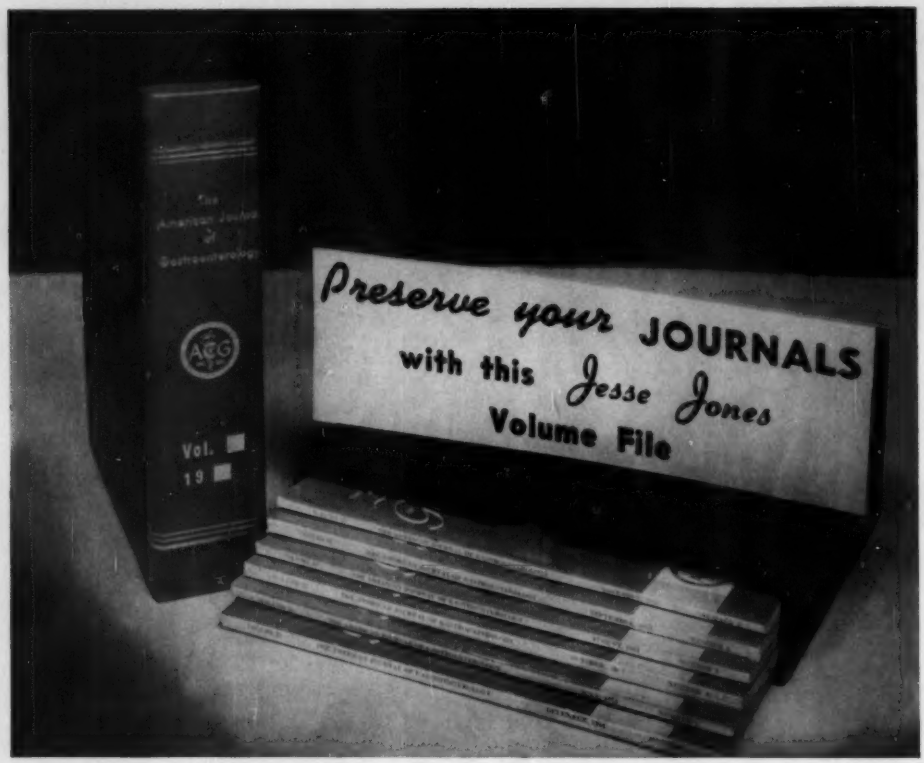

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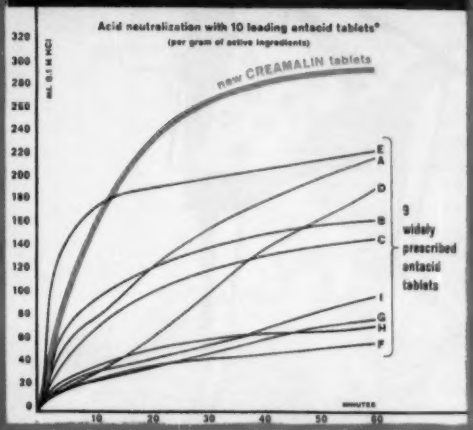

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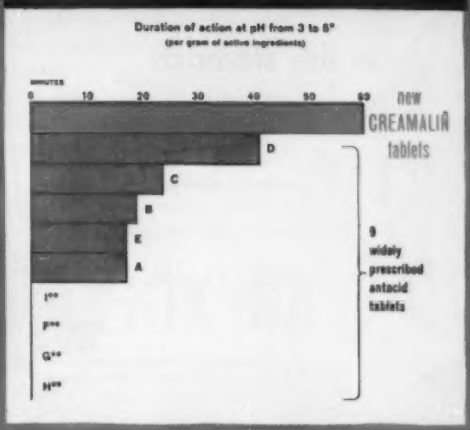

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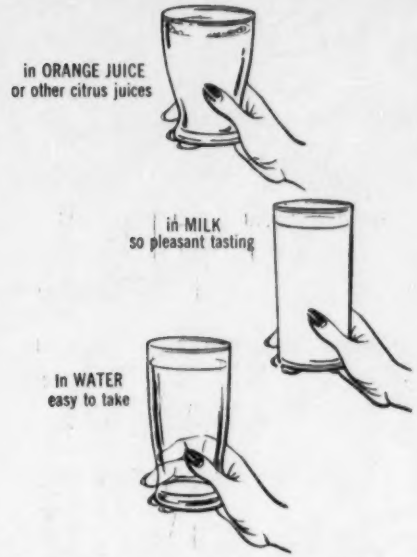
TRADEMARK: KOLANTYL®

L. A.* FORMULA*



the truly palatable bowel NORMALIZER

to provide your patients with the smooth bulk so essential to normal bowel function

L. A. FORMULA substitutes a moist smooth bulk for the fibrous, irritating bulk of uncertain consistency which results from the average diet. L. A. FORMULA disperses intimately with the intestinal contents to form a softly compact, well-formed stool of normal consistency which clears the rectum completely and easily.

**Abbreviation for the Latin "Levis Amplitudo", meaning smooth bulk.*

**Refined psyllium hydrophilic mucilloid with lactose and dextrose.*

Your Patients will appreciate the modest cost!

SAMPLES AVAILABLE PROMPTLY UPON REQUEST

Made by BURTON, PARSONS & COMPANY, *Since 1932*
Originators of Fine Hydrophilic Colloids
Washington 9, D. C.

NOW many more hypertensive patients may have THE FULL BENEFITS OF CORTICOSTEROID THERAPY

Except for one case of mild blood-pressure elevation (150/90) **no hypertension was seen in any of 1500 patients**† as a result of treatment with DECADRON—the new and, on a milligram basis, most potent of all corticosteroids. **Hypertension induced by other steroids diminished or disappeared.**

Thus with DECADRON, hypertension no longer appears to be a contraindication to successful corticosteroid therapy. And the dramatic therapeutic impact of DECADRON was virtually unmarred by diabetogenic or psychic reactions . . . Cushingoid effects were fewer and milder . . . and there were no new or "peculiar" side effects. Moreover, DECADRON helped restore a "natural" sense of well-being.

†Analysis of clinical reports.

Decadron*

DEXAMETHASONE

treats more patients more effectively

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